Cochrane Library

Cochrane Database of Systematic Reviews

Systemic corticosteroids for the treatment of COVID-19 (Review)

Wagner C, Griesel M, Mikolajewska A, Mueller A, Nothacker M, Kley K, Metzendorf MI, Fischer AL, Kopp M, Stegemann M, Skoetz N, Fichtner F

Wagner C, Griesel M, Mikolajewska A, Mueller A, Nothacker M, Kley K, Metzendorf M-I, Fischer A-L, Kopp M, Stegemann M, Skoetz N, Fichtner F.
Systemic corticosteroids for the treatment of COVID-19.
Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD014963.
DOI: 10.1002/14651858.CD014963.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Systemic corticosteroids for the treatment of COVID-19

Carina Wagner[1a], Mirko Griesel[2b], Agata Mikolajewska[3], Anika Mueller[4], Monika Nothacker[5], Karoline Kley[2], Maria-Inti Metzendorf[6], Anna-Lena Fischer[7], Marco Kopp[1], Miriam Stegemann[3], Nicole Skoetz[8c], Falk Fichtner[2d]

[1]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [2]Department of Anaesthesiology and Intensive Care, University of Leipzig Medical Center, Leipzig, Germany. [3]Department of Infectious Diseases and Respiratory Medicine, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [4]Department of Anesthesiology and Intensive Care Medicine, Campus Charité Mitte and Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany. [5]AWMF Institute for Medical Knowledge Management, Marburg, Germany. [6]Cochrane Metabolic and Endocrine Disorders Group, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany. [7]Department of Anaesthesia and Intensive care, Universitätsklinikum Leipzig, 04103 Leipzig, Germany. [8]Cochrane Cancer, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[a]contributed equally (first author). [b]contributed equally (first author). [c]contributed equally (last author). [d]contributed equally (last author)

Contact: Nicole Skoetz, nicole.skoetz@uk-koeln.de.

Editorial group: Cochrane Haematology Group.
Publication status and date: New, published in Issue 8, 2021.

Citation: Wagner C, Griesel M, Mikolajewska A, Mueller A, Nothacker M, Kley K, Metzendorf M-I, Fischer A-L, Kopp M, Stegemann M, Skoetz N, Fichtner F. Systemic corticosteroids for the treatment of COVID-19. *Cochrane Database of Systematic Reviews* 2021, Issue 8. Art. No.: CD014963. DOI: 10.1002/14651858.CD014963.

ABSTRACT

Background

Systemic corticosteroids are used to treat people with COVID-19 because they counter hyper-inflammation. Existing evidence syntheses suggest a slight benefit on mortality. So far, systemic corticosteroids are one of the few treatment options for COVID-19. Nonetheless, size of effect, certainty of the evidence, optimal therapy regimen, and selection of patients who are likely to benefit most are factors that remain to be evaluated.

Objectives

To assess whether systemic corticosteroids are effective and safe in the treatment of people with COVID-19, and to keep up to date with the evolving evidence base using a living systematic review approach.

Search methods

We searched the Cochrane COVID-19 Study Register (which includes PubMed, Embase, CENTRAL, ClinicalTrials.gov, WHO ICTRP, and medRxiv), Web of Science (Science Citation Index, Emerging Citation Index), and the WHO COVID-19 Global literature on coronavirus disease to identify completed and ongoing studies to 16 April 2021.

Selection criteria

We included randomised controlled trials (RCTs) that evaluated systemic corticosteroids for people with COVID-19, irrespective of disease severity, participant age, gender or ethnicity.

We included any type or dose of systemic corticosteroids. We included the following comparisons: systemic corticosteroids plus standard care versus standard care (plus/minus placebo), dose comparisons, timing comparisons (early versus late), different types of corticosteroids and systemic corticosteroids versus other active substances.

We excluded studies that included populations with other coronavirus diseases (severe acute respiratory syndrome or Middle East respiratory syndrome), corticosteroids in combination with other active substances versus standard care, topical or inhaled corticosteroids, and corticosteroids for long-COVID treatment.

Data collection and analysis

We followed standard Cochrane methodology. To assess the risk of bias in included studies, we used the Cochrane 'Risk of bias' 2 tool for RCTs. We rated the certainty of evidence using the GRADE approach for the following outcomes: all-cause mortality, ventilator-free days, new need for invasive mechanical ventilation, quality of life, serious adverse events, adverse events, and hospital-acquired infections.

Main results

We included 11 RCTs in 8075 participants, of whom 7041 (87%) originated from high-income countries. A total of 3072 participants were randomised to corticosteroid arms and the majority received dexamethasone (n = 2322). We also identified 42 ongoing studies and 16 studies reported as being completed or terminated in a study registry, but without results yet.

Hospitalised individuals with a confirmed or suspected diagnosis of symptomatic COVID-19

Systemic corticosteroids plus standard care versus standard care plus/minus placebo

We included 10 RCTs (7989 participants), one of which did not report any of our pre-specified outcomes and thus our analysis included outcome data from nine studies.

All-cause mortality (at longest follow-up available): systemic corticosteroids plus standard care probably reduce all-cause mortality slightly in people with COVID-19 compared to standard care alone (median 28 days: risk difference of 30 in 1000 participants fewer than the control group rate of 275 in 1000 participants; risk ratio (RR) 0.89, 95% confidence interval (CI) 0.80 to 1.00; 9 RCTs, 7930 participants; moderate-certainty evidence).

Ventilator-free days: corticosteroids may increase ventilator-free days (MD 2.6 days more than control group rate of 4 days, 95% CI 0.67 to 4.53; 1 RCT, 299 participants; low-certainty evidence). Ventilator-free days have inherent limitations as a composite endpoint and should be interpreted with caution.

New need for invasive ventilation: the evidence is of very low certainty. Because of high risk of bias arising from deaths that occurred before ventilation we are uncertain about the size and direction of the effects. Consequently, we did not perform analysis beyond the presentation of descriptive statistics.

Quality of life/neurological outcome: no data were available.

Serious adverse events: we included data on two RCTs (678 participants) that evaluated systemic corticosteroids compared to standard care (plus/minus placebo); for *adverse events and hospital-acquired infections*, we included data on five RCTs (660 participants). Because of high risk of bias, heterogeneous definitions, and underreporting we are uncertain about the size and direction of the effects. Consequently, we did not perform analysis beyond the presentation of descriptive statistics (very low-certainty evidence).

Different types, dosages or timing of systemic corticosteroids

We identified one study that compared methylprednisolone with dexamethasone. The evidence for mortality and new need for invasive mechanical ventilation is very low certainty due to the small number of participants (n = 86). No data were available for the other outcomes.

We did not identify comparisons of different dosages or timing.

Outpatients with asymptomatic or mild disease

Currently, there are no studies published in populations with asymptomatic infection or mild disease.

Authors' conclusions

Moderate-certainty evidence shows that systemic corticosteroids probably slightly reduce all-cause mortality in people hospitalised because of symptomatic COVID-19. Low-certainty evidence suggests that there may also be a reduction in ventilator-free days. Since we are unable to adjust for the impact of early death on subsequent endpoints, the findings for ventilation outcomes and harms have limited applicability to inform treatment decisions. Currently, there is no evidence for asymptomatic or mild disease (non-hospitalised participants).

There is an urgent need for good-quality evidence for specific subgroups of disease severity, for which we propose level of respiratory support at randomisation. This applies to the comparison or subgroups of different types and doses of corticosteroids, too. Outcomes apart from mortality should be measured and analysed appropriately taking into account confounding through death if applicable.

We identified 42 ongoing and 16 completed but not published RCTs in trials registries suggesting possible changes of effect estimates and certainty of the evidence in the future. Most ongoing studies target people who need respiratory support at baseline. With the living approach of this review, we will continue to update our search and include eligible trials and published data.

PLAIN LANGUAGE SUMMARY

Are corticosteroids (anti-inflammatory medicines) given orally or by injection an effective treatment for people with COVID-19?

Key messages

• Corticosteroids (anti-inflammatory medicines) given orally or by injection (systemic) are probably effective treatments for people hospitalised with COVID-19. We don't know whether they cause unwanted effects.

• We don't know which systemic corticosteroid is the most effective. We found no evidence about people without symptoms or with mild COVID-19 who were not hospitalised.

• We found 42 ongoing studies and 16 completed studies that have not published their results. We will update this review when we find new evidence.

What are corticosteroids?

Corticosteroids are anti-inflammatory medicines that reduce redness and swelling. They also reduce the activity of the immune system, which defends the body against disease and infection. Corticosteroids are used to treat a variety of conditions, such as asthma, eczema, joint strains and rheumatoid arthritis.

Systemic corticosteroids can be swallowed or given by injection to treat the whole body. High doses of corticosteroids taken over a long time may cause unwanted effects, such as increased appetite, difficulty sleeping and mood changes.

Why are corticosteroids possible treatments for COVID-19?

COVID-19 affects the lungs and airways. As the immune system fights the virus, the lungs and airways become inflamed, causing breathing difficulties. Corticosteroids reduce inflammation, so may reduce the need for breathing support with a ventilator (a machine that breathes for a patient). Some patients' immune systems overreact to the virus causing further inflammation and tissue damage; corticosteroids may help to control this response.

What did we want to find out?

We wanted to know whether systemic corticosteroids are an effective treatment for people with COVID-19 and whether they cause unwanted effects.

We were interested in:

• deaths from any cause up to 14 days after treatment, or longer if reported;
• whether people got better or worse after treatment, based on their need for breathing support;
• quality of life;
• unwanted effects and infections caught in hospital.

What did we do?

We searched for studies that investigated systemic corticosteroids for people with mild, moderate or severe COVID-19. People could be any age, sex or ethnicity.

Studies could compare:

• corticosteroids plus usual care versus usual care with or without placebo (sham medicine);
• one corticosteroid versus another;
• corticosteroids versus a different medicine;
• different doses of a corticosteroid; or
• early versus late treatment.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 11 studies with 8075 people. About 3000 people received corticosteroids, mostly dexamethasone (2322 people). Most studies took place in high-income countries.

We also found 42 ongoing studies, and 16 completed studies that have not yet published their results.

Main results

Ten studies compared corticosteroids plus usual care versus usual care with or without placebo. Only one study compared two corticosteroids. The studies included only hospitalised people with confirmed or suspected COVID-19. No studies looked at non-hospitalised people, different doses or timing, or provided information about quality of life.

Corticosteroids plus usual care compared to usual care with or without placebo (10 studies)

• Corticosteroids probably reduce the number of deaths from any cause slightly, up to 60 days after treatment (9 studies, 7930 people).
• One study (299 people) reported that people on a ventilator at the start of the study were ventilation-free for more days with corticosteroids than with usual care, so corticosteroids may improve people's symptoms.
• Four studies (427 people) reported whether people not on a ventilator at the start of treatment later needed to be put on a ventilator, but we could not pool the studies' results, so we are unsure if people's symptoms get worse with corticosteroids or usual care.
• We don't know if corticosteroids increase or reduce serious unwanted effects (2 studies, 678 people), any unwanted effects (5 studies, 660 people), or infections caught in hospital (5 studies, 660 people).

Methylprednisolone versus dexamethasone (1 study, 86 people)

• We don't know whether the corticosteroid methylprednisolone reduces the number of deaths from any cause compared to dexamethasone in the 28 days after treatment.
• We don't know if methylprednisolone worsens people's symptoms compared to dexamethasone, based on whether they needed ventilation in the 28 days after treatment.
• The study did not provide information about anything else we were interested in.

What are the limitations of the evidence?

We are moderately confident in the evidence about corticosteroids' effect on deaths from any cause. However, our confidence in the other evidence is low to very low, because studies did not use the most robust methods, and the way results were recorded and reported differed across studies. We did not find any evidence on quality of life and there was no evidence from low-income countries or on people with mild COVID-19 or no symptoms, who were not hospitalised.

How up to date is this evidence?

Our evidence is up to date to 16 April 2021.

Summary of findings 1. Summary of Findings Table - Systemic corticosteroids plus standard care compared to standard care for adults with a suspected or confirmed diagnosis of COVID-19

Systemic corticosteroids plus standard care compared to standard care for adults with a suspected or confirmed diagnosis of COVID-19

Patient or population: adults with a suspected or confirmed diagnosis of COVID-19 **Setting**: inpatient, ICU **Intervention**: systemic corticosteroids plus standard care **Comparison**: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with systemic corticosteroids plus standard care				
All-cause mortality follow up: range 21 days to 60 days	275 per 1000	**245 per 1000** (220 to 275)	**RR 0.89** (0.80 to 1.00)	7930 (9 RCTs)	⊕⊕⊕⊖ MODERATE [a]	Systemic corticosteroids probably reduce all-cause mortality slightly.
Clinical improvement: ventilator-free days follow up: 28 days	The mean clinical improvement: ventilator-free days was **4** days	MD **2.6 days more** (0.67 more to 4.53 more)	-	299 (1 RCT)	⊕⊕⊖⊖ LOW [b]	Systemic corticosteroids may increase ventilator-free days.
Clinical worsening: new need for IMV follow up: 28 days	We did not perform meta-analyses because of high risk of bias arising from deaths that occurred before ventilation. We present descriptive data with effects below 1 in favour of corticosteroids: Corral-Gudino 2021: RR 0.98 (95% CI 0.52, 1.85); Edalatifard 2020: RR 0.14 (95% CI 0.03, 0.56); Jamaati 2021: RR 1.18 (95% CI 0.66, 2.11); Jeronimo 2020: RR 0.99 (95% CI 0.56, 1.76).			427 (4 RCTs)	⊕⊖⊖⊖ VERY LOW [c]	
Quality of life, including fatigue and neurological status - not reported	-	-	-	-	-	No study reported this outcome.
Serious adverse events (follow	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. Therefore, we only present descriptive statistics with effects below 1 in favour of corticosteroids: Angus			678 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [d]	

up: during treatment)	2020 shock-dependent hydrocortisone: RR 4.11 (95% CI 0.23, 72.98); Angus 2020 fixed-dose hydrocortisone: RR 1.43 (95% CI 0.16, 12.49); Tomazini 2020: RR 0.54 (95% CI 0.19, 1.59).		
Adverse events (follow up: during treatment)	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. We only present descriptive statistics with effects below 1 in favour of corticosteroids: Corral-Gudino 2021: RR 11.60 (95% CI 1.62, 83.03); Dequin 2020: RR 0.77 (95% CI 0.59, 1.00); Edalatifard 2020: RR 0.82 (95% CI 0.12, 5.48); Tang 2021: RR 0.63 (95% CI 0.22, 1.76); Tomazini 2020: RR 0.69 (95% CI 0.50, 0.96).	660 (5 RCTs)	⊕⊖⊖⊖ VERY LOW [e]
Hospital-acquired infections (follow up: during treatment)	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. We present descriptive statistics only: Corral-Gudino 2021: RR 4.14 (95% CI 0.51, 33.49); Dequin 2020: RR 0.77 (95% CI 0.59, 1.00); Edalatifard 2020: RR 2.49 (95% CI 0.11, 58.74); Tang 2021: RR 2.00 (95% CI 0.19, 21.24); Tomazini 2020: RR 0.75 (95% CI 0.52, 1.09).	660 (5 RCTs)	⊕⊖⊖⊖ VERY LOW [f]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_424096272361428897.

a. We downgraded for risk of bias for deviation from intended interventions (Angus 2020; Edalatifard 2020; Horby 2021; Jeronimo 2020; Tomazini 2020), for selective reporting (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Jamaati 2021), for missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), for baseline differences (Jamaati 2021) and indirectness (mortality observed at 21 to 60 days, in most studies at 28 days should be seen as a proxy for long-term survival as long as we are unsure about its predictive value; 1 point altogether).
b. We downgraded because of risk of bias through deviation from intended interventions (Tomazini 2020; 1 point), and imprecision (broad confidence interval, low number of evaluated participants, 1 point).
c. We downgraded because of risk of bias for mainly for problems with deviations from intended interventions (Edalatifard 2020; Jeronimo 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), baseline differences (Jamaati 2021), missing pre-specification (Corral-Gudino 2021; Edalatifard 2020; Jamaati 2021; Jeronimo 2020), missing adjustment for competing risk (Corral-Gudino 2021; Edalatifard 2020; Jamaati 2021; Jeronimo 2020) (2 points), and imprecision (fewer than 500 events, 1 point).
d. We downgraded for risk of bias for deviations from intended interventions (Angus 2020; Tomazini 2020), missing adjustment for competing risk (Angus 2020; Tomazini 2020; 2 points), publication bias because 2 out 10 studies including the largest, Horby 2021, did not report this major safety outcome (downgrade 1 point), and imprecision (fewer than 500 events, downgrade 1 point).

e. We downgraded because of risk of bias mainly through deviation from intended intervention (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020) and selection of adverse events usually associated with steroids (Corral-Gudino 2021; Edalatifard 2020; Tang 2021, 2 points), imprecision (fewer than 500 events, 1 point), and publication bias (only 5 out of 10 reported this established safety outcome, 1 point)
f. We downgraded because of risk of bias mainly from deviation from intended interventions (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), missing pre-specification of its definition (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021, 2 points), imprecision (fewer than 500 events, 1 point), and publication bias (only 5 out of 10 studies reported this outcome which represents an adverse event, 1 point).

Summary of findings 2. Summary of Findings Table - Methylprednisolone compared to dexamethasone for adults with a suspected or confirmed diagnosis of COVID-19

Methylprednisolone compared to dexamethasone for adults with a suspected or confirmed diagnosis of COVID-19

Patient or population: adults with a suspected or confirmed diagnosis of COVID-19 **Setting**: inpatient, ICU **Intervention**: methylprednisolone **Comparison**: dexamethasone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with dexamethasone	Risk with methylprednisolone				
All-cause mortality follow up: 28 days	357 per 1000	**182 per 1000** (86 to 382)	**RR 0.51** (0.24 to 1.07)	86 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a]	We are uncertain whether methylprednisolone can decrease all-cause mortality directly compared to dexamethasone. Additionally, 28-day mortality should be understood as a proxy for sustained survival.
Clinical improvement: ventilator-free days - not reported	-	-	-	-	-	No study reported this outcome.
Clinical worsening: new need for IMV follow up: 28 days	There is high risk of bias for deaths that occurred before ventilation. Therefore we only present descriptive statistics: Ranjbar 2021: RR 0.48 (95% CI 0.23, 1.00).			86 (1 RCT)	⊕⊖⊖⊖ VERY LOW [b]	
Quality of life, including fatigue and neurological status - not reported	-	-	-	-	-	No study reported this outcome.

Serious adverse events - not reported	-	-	-	-	-	No study reported this outcome.
Adverse events - not reported	-	-	-	-	-	No study reported this outcome.
Hospital-acquired infections - not reported	-	-	-	-	-	No study reported this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_424391243004646489.

a. We downgraded for risk of bias for missing pre-specification/protocol/statistical analysis plan (1 point), and serious imprecision (fewer than 50 events, 2 points).
b. We downgraded for risk of bias for missing data/adjustment for competing risk and missing protocol/statistical analysis plan (1 point), and serious imprecision (fewer than 50 events, 2 points)

BACKGROUND

This work is part of a series of Cochrane Reviews investigating treatments and therapies for coronavirus disease 2019 (COVID-19). Reviews in this series share information in the background section and methodology with the first published reviews about monoclonal antibodies (Kreuzberger 2021), and convalescent plasma (Piechotta 2021), from the German research project "CEOsys" (COVID-19 Evidence Ecosystem).

Description of the condition

COVID-19 is a rapidly spreading infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). On 11 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak a pandemic. The severity of COVID-19 is unprecedented in comparison to that of previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which caused 813 and 858 deaths, respectively (WHO 2007; WHO 2019). Despite intensive international efforts to contain its spread, SARS-CoV-2 has resulted in a continuously rising number of cases and deaths with a clearly accelerating increase in the first months of 2021 (WHO 2021a; WHO 2021b). In the meantime, the appearance of SARS-CoV-2 variants with higher transmissibility is further increasing infection rates (WHO 2021c).

The risk for a severe course of disease, hospitalisation and mortality is higher among individuals aged 65 years or older, smokers and those with certain underlying medical conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart conditions, immunocompromised state, obesity, sickle cell disease or type 2 diabetes mellitus (Huang 2020; Liang 2020; WHO 2020a; Williamson 2020). COVID-19 case fatality ratios vary widely between countries and reporting periods, from 0.0% to more than 25% (Johns Hopkins University 2021). However, these numbers may be misleading as they tend to overestimate the infection fatality ratio due to varying testing frequency, a lack of reporting dates, and variations in case definitions, especially in the beginning of the pandemic when the main focus was on severe cases (WHO 2020b).

The median incubation time is estimated to be five to six days, and 97.5% of symptomatic cases develop symptoms within 11.5 days of exposure (Lauer 2020). Sore throat, cough, fever, headache, fatigue, and myalgia or arthralgia are the most commonly reported symptoms (Struyf 2020). Other symptoms include dyspnoea, chills, nausea or vomiting, diarrhoea, and nasal congestion (WHO 2020a). The majority of infected people (approximately 80%) have mild symptoms (Wu 2020), or remain completely asymptomatic (Buitrago-Garcia 2020). A smaller proportion (approximately 14%) are affected by severe or critical disease that requires treatment at an intensive care unit (ICU) due to respiratory failure, septic shock or multiple organ dysfunction (Wu 2020). In light of the extent of the COVID-19 pandemic and the scarcity of effective treatments, there is an urgent need for effective therapies to save lives and to reduce the high burden on healthcare systems, especially in the face of evolving variants of the virus with the potential for increased transmissibility and the limited global availability of vaccines.

Description of the intervention

Corticosteroids are a group of stress hormones produced from the adrenal cortex. In addition to their stress-mediated mechanisms for generating energy substrates, corticosteroids have anti-inflammatory and immunosuppressive properties in higher doses and are applied in a wide variety of ways in almost all fields of medicine (Barnes 2006; Rhen 2005). For example, corticosteroids are used at high doses of more than 6 mg/kg up to 30 mg/kg methylprednisolone corresponding to more than 30 mg/kg up to 150 mg/kg hydrocortisone equivalents daily for short-term, high-dose pulse therapy against solid organ transplant rejection, or about 0.5 mg/kg hydrocortisone equivalents daily for prolonged therapy in different inflammatory lung diseases. A major representative of synthetic corticosteroids is the long-acting compound dexamethasone. Examples of other synthetic corticosteroids with weaker and shorter activity are methylprednisolone and hydrocortisone (Bourdeau 2003). To obtain comparable effects, dosage equivalents are needed for the different corticosteroids.

How the intervention might work

It has been proposed that corticosteroids could be clinically effective against severe and critical COVID-19. A substantial percentage of patients develop severe and critical COVID-19 that requires hospitalisation, with dyspnoea, hypoxia, or relevant lung involvement based on imaging, as well as respiratory failure, shock, or multi-organ dysfunction requiring ventilator support (Thibeault 2021; Wu 2020). In COVID-19, an insufficient host defence and unbalanced inflammation is thought to play a key role in the pathophysiology of hypoxemic respiratory failure (Schulte-Schrepping 2020). A systemic inflammatory response with the excessive release of cytokines and inflammation mediators can lead to lung injury with the development of acute respiratory distress syndrome (ARDS). The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects by modulating cytokine release (Villar 2020). Corticosteroids have been widely used in syndromes closely related to COVID-19, including SARS, MERS, severe influenza, and community-acquired pneumonia. However, the evidence to support or discourage the use of corticosteroids under these conditions has been weak. Corticosteroids can induce harm through immunosuppressive effects during the treatment of infection. In SARS-CoV-2 infection, viral shedding appears early in the illness and declines thereafter. The effect of corticosteroid therapy on virus clearance in COVID-19 needs to be taken into consideration. In acutely critically ill people, dexamethasone has comparatively few side effects (Rochwerg 2018). However, patients may suffer from blood glucose problems and potential fungal infections. The therapeutic use of higher doses of corticosteroids over a longer time suppresses the hypothalamic-pituitary-adrenal axis such that dosage-tapering may be needed.

Why it is important to do this review

Extensive work has been done in the field of systematic reviews regarding COVID-19 interventions, including corticosteroids. For example, several systematic reviews investigated the association between the use of corticosteroids and COVID-19-related mortality based on randomised controlled trials (RCT) and non-randomised studies (e.g. Sterne 2020; Van Paassen 2020). This Cochrane review will fill current gaps by identifying, describing, evaluating, and meta-analysing RCTs of systemic corticosteroids in relation to

clinical outcomes in COVID-19. Unlike other systematic reviews in this field, it considers the outcome clinical improvement and worsening (defined by respiratory support) as well as subgroup analysis. The living systematic review will be updated once new evidence becomes available.

OBJECTIVES

To assess whether systemic corticosteroids are effective and safe in the treatment of people with COVID-19, and to keep up-to-date with the evolving evidence base using a living systematic review approach.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on Cochrane Haematology's standard template and is in line with a series of Cochrane Reviews investigating treatments and therapies against COVID-19. We made specific adaptations related to the research question if necessary. The protocol for this review was registered with PROSPERO on 21 December 2020 (Wagner 2021).

To assess the efficacy and safety of systemic corticosteroids against COVID-19, we included RCTs, as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly controlled therapeutic settings. We used the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions and outcomes:

- full-text publications;
- preprint articles.

We included preprints for a complete overview of the ongoing research activity, especially for tracking newly emerging studies about systemic corticosteroids against COVID-19. We did not apply any limitation with respect to the length of follow-up.

Types of participants

We included adults with a suspected or confirmed diagnosis of COVID-19 (as described in the study) and we did not exclude any studies based on gender, ethnicity, disease severity, or setting.

We excluded studies evaluating corticosteroids against coronavirus diseases such as SARS or MERS, or other viral diseases, such as influenza. If studies enrolled populations with or exposed to mixed viral diseases, we had planned to only include these if study authors provided subgroup data for SARS-CoV-2 infection.

Types of interventions

We included the following interventions:

- any type or dose of systemic corticosteroids;
- oral or intravenous application.

We included the following comparisons:

- systemic corticosteroids plus standard care versus standard care (plus/minus placebo);
- dose comparisons;
- timing comparisons (early versus late);
- different types of corticosteroids;
- systemic corticosteroid versus other active substances.

Standard care in both arms should be similar.

We excluded the following interventions:

- corticosteroid plus other active substance versus standard care;
- topical corticosteroids;
- inhaled corticosteroids;
- corticosteroids for long-COVID treatment.

Types of outcome measures

We evaluated core outcomes in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020; Marshall 2020), and additional outcomes that have been prioritised by consumer representatives and the German guideline panel for inpatient therapy against COVID-19.

We defined this outcome set for hospitalised individuals with a confirmed or suspected diagnosis of COVID-19 and moderate to severe disease, according to WHO clinical progression scale stage 4 to 9 (Marshall 2020), that is, all patients who were hospitalised because of symptomatic COVID-19 treated with all different levels of respiratory support (no additional oxygen, low-flow oxygen prongs or mask ('low-flow oxygen' only hereafter), high-flow oxygen or non-invasive ventilation, invasive mechanical ventilation including extracorporeal membrane oxygenation (ECMO)), and individuals with a confirmed or suspected diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to the WHO clinical progression scale (Marshall 2020). Of note, readers may encounter respiratory support both as a baseline characteristic and as an outcome measure - in the latter case we used changes in the level of support.

Individuals with a suspected or confirmed diagnosis of COVID-19 and moderate to severe disease

Prioritised outcomes (included in the summary of findings table)

- Mortality: all-cause mortality at day 14 or any longer observation period, in-hospital all-cause mortality
- Improvement of clinical status during the longest observation period available:
  - ventilator-free days
- Deterioration of clinical status during the longest observation period available:
  - new need for invasive mechanical ventilation, that is, transition to WHO 7 to 9 if 6 or lower at baseline (see Figure 1). If new need was not available directly, we used death as a proxy for assumed intubation counted together with patients alive and ventilated.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) during the longest period available

- Serious adverse events, defined as the number of participants with any event
- Adverse events (any grade), defined as the number of participants with any event
- Hospital-acquired infections

Figure 1. WHO Clinical Progression Scale (Marshall 2020). Copyright © 2020 Elsevier Ltd. All rights reserved: reproduced with permission. ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; NIV = non-invasive ventilation; pO_2 = partial pressure of oxygen; RNA = ribonucleic acid; SpO_2 = oxygen saturation. *If hospitalised for isolation only, record status for ambulatory patients.

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Additional outcomes (not included in the summary of findings table)

- Liberation from invasive mechanical ventilation in patients, that is, transition to WHO 6 or lower if 7 or higher at baseline (see Figure 1). If liberation was not available directly, we used death as a proxy for assumed non-liberation counted together with patients alive and ventilated
- Need for dialysis during the longest period available
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days

Individuals with a suspected or confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

Prioritised outcomes (included in the summary of findings table)

- Mortality: all-cause mortality at day 14 or any longer observation period, in-hospital all-cause mortality
- Improvement of clinical status during the longest observation period available:
  - ventilator-free days
- Deterioration of clinical status during the longest observation period available:
  - new need for invasive mechanical ventilation, that is, transition to WHO 7 to 9 if 6 or lower at baseline (see Figure 1). If new need was not available directly, we used death as a proxy for assumed intubation counted together with patients alive and ventilated.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) during the longest period available
- Serious adverse events, defined as the number of participants with any event
- Adverse events (any grade), defined as the number of participants with any event
- Infections

Additional outcomes (not included in the summary of findings table)

- Liberation from invasive mechanical ventilation in patients, that is, transition to WHO 6 or lower if 7 or higher at baseline (see Figure 1). If liberation was not available directly, we used

death as a proxy for assumed non-liberation counted together with patients alive and ventilated
- Need for dialysis during the longest period available
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days

Timing of outcome measurement

In the case of time-to-event analysis, for example, for time to clinical improvement, we included the outcome measure based on the longest follow-up time. We also collected information on outcomes from all other time points reported in the publications.

Search methods for identification of studies

Electronic searches

Our information specialist (MIM) conducted systematic searches in the following sources from the inception of each database to 16 April 2021 (search date for all databases) and did not place restrictions on the language of publication.

- Cochrane COVID-19 Study Register (www.covid-19.cochrane.org), comprising:
  - MEDLINE (PubMed), daily updates;
  - Embase.com, weekly updates;
  - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
  - WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates;
  - medRxiv (www.medrxiv.org), weekly updates;
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates.
- Web of Science Core Collection (Clarivate), from 1 January 2020 onwards:
  - Science Citation Index Expanded (1945 to present);
  - Emerging Sources Citation Index (2015 to present).
- WHO COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).

Database search results for Web of Science were restricted to publications from 2020 to the present date, as no treatment studies on COVID-19 were registered prior to January 2020. For detailed search strategies, see Appendix 1.

Searching other resources

We identified other potentially eligible studies or ancillary publications by searching the reference lists of included studies and systematic reviews.

We searched for grey literature, which we defined as searching study registries such as ClinicalTrials.gov and WHO ICTRP contained in the Cochrane COVID-19 Study Register, as well as searching preprint servers and grey literature indexes contained in the Cochrane COVID-19 Study Register and the WHO COVID-10 Global literature on coronavirus disease.

Data collection and analysis

Selection of studies

Two review authors (NS, CW) independently screened the results of the search strategies for eligibility for this review by reading the titles and abstracts using EndNote Software (EndNote X9). We coded the abstracts as either 'include' or 'exclude'. In the case of disagreement or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, they consulted the third review author to reach a final decision.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and showed the total numbers of retrieved references and the numbers of included and excluded studies. We listed all studies that we excluded after full-text assessment and the reasons for their exclusion in the Characteristics of excluded studies section.

Data extraction and management

We conducted data extraction according to the guidelines proposed by Cochrane (Li 2021). Two out of five review authors (AM, MG, CW, AF, KK) extracted data independently and in duplicate, using a customised data extraction form developed in Microsoft Excel (Microsoft 2018). We resolved disagreements by discussion. If we were unable to reach agreement, we involved a third review author.

Two out of three review authors (MG, MK, CW) independently assessed eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias. If the review authors were unable to reach a consensus, they consulted a third review author.

We extracted the following information if reported.

- General information: author, title, source, publication date, country, language, duplicate publications
- Study characteristics: trial design, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, number of participants with positive, negative or unknown RT-PCR test result, additional diagnoses, severity of disease, previous treatments, concurrent treatments, co-morbidities (e.g. diabetes, immunosuppression)
- Interventions: type of corticosteroid, dose, frequency, timing, duration and route of administration, setting (e.g. inpatient, outpatient), duration of follow-up
- Control interventions: placebo, no treatment or other intervention; dose, frequency, timing, duration and route of administration, setting, duration of follow-up
- Outcomes: as specified under Types of outcome measures
- Risk of bias assessment: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results.

Assessment of risk of bias in included studies

We used the Risk of Bias 2 (RoB 2) tool (version of 22 August 2019) to analyse the risk of bias of study results (Sterne 2019). Of interest for this review is the effect of the assignment to the intervention (the

intention-to-treat (ITT) effect), thus, we performed all assessments with RoB 2 on this effect. The outcomes that we assessed are those specified for inclusion in the summary of findings table.

Two out of three review authors (MK, MG, CW) independently assessed the risk of bias for each outcome. In case of discrepancies among their judgements and inability to reach consensus, we consulted the fourth review author to reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b):

- bias arising from the randomisation process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome;
- bias in selection of the reported result.

To address these types of bias we used the signalling questions recommended in RoB 2 and made a judgement using the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- Probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- 'Probably no': a judgement has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No information': if the study report does not provide sufficient information to allow any judgement.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias:

- low risk of bias;
- some concerns;
- high risk of bias.

Subsequently, we derived an overall risk of bias rating for each pre-specified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judge the trial to be at low risk of bias for all domains for this result.
- 'Some concerns': we judge the trial to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result, or we judge the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (available on the riskofbias.info website), stored, and presented our detailed RoB 2 assessments in the analyses section and as supplementary online material.

As we collected the data from the studies and assessed RoB 2, we noticed an issue with competing risk of death (Columbia Public Health 2021 as easily accessible introduction), which we discussed in Quality of the evidence. We dealt with this issue within domain 3 of RoB 2 (Higgins 2019).

Measures of treatment effect

For continuous outcomes, we recorded the mean, standard deviation (SD) and total number of participants in both treatment and control groups. Where continuous outcomes used the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we performed analyses using the standardised mean difference (SMD). For interpreting SMDs, we re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact (e.g. clinical symptoms with the WHO Clinical Progression Scale (WHO 2020c)).

For dichotomous outcomes, we recorded the number of events and total number of participants in both treatment and control groups. We reported the pooled risk ratio (RR) with a 95% CI (Deeks 2021).

If available, we planned to extract and report hazard ratios (HRs) for time-to-event outcomes (e.g. time to liberation from invasive ventilation). If HRs were not available, we would make every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney (Parmar 1998; Tierney 2007).

Unit of analysis issues

The aim of this review is to summarise studies that analyse data at the level of the individual. We would also have accepted cluster-randomised trials for inclusion, had we found any. We collated multiple reports of one study so that the study, and not the report, is the unit of analysis.

Studies with multiple treatment groups

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021c), for studies with multiple treatment groups of the same intervention (i.e. dose, route of administration), we planned to evaluate whether study arms were sufficiently homogeneous to be combined. If arms could not be pooled, we planned to compare each arm with the common comparator separately. For pair-wise meta-analysis, we planned to split the 'shared' group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, we planned to divide both the number of events and the total number of participants, and for continuous outcomes, we planned to divide the total number of participants with unchanged means and SDs.

Dealing with missing data

Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we took into account at study level, at outcome level and at summary data level (Deeks 2021). At all levels, it is important to differentiate between data 'missing at random', which may often

be unbiased, and 'not missing at random', which may bias study and thus review results.

We requested missing data for four outcomes from the corresponding authors via email, followed by a second email and a phone call attempt if necessary. The outcomes were mortality during the longest observation period, need for invasive ventilation, liberation from invasive ventilation and adverse events. We contacted authors from 10 included studies (Angus 2020; Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Farahani 2021; Horby 2021; Jamaati 2021; Jeronimo 2020; Ranjbar 2021; Tang 2021). Of these, three authors sent in the requested data (Corral-Gudino 2021; Edalatifard 2020; Jeronimo 2020) and one (Tomazini 2020), had already provided all necessary data in the publication. We have not yet requested detailed individual time-to-event data from the study authors, which would be necessary to adjust for competing risks. Alternatively, data already adjusted by the study authors themselves could be presented, too, in a future version of this review.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. We used the I^2 statistic (Higgins 2003), and visual examination, to assess possible heterogeneity (I^2 statistic > 30% to signify moderate heterogeneity, I^2 statistic > 75% to signify considerable heterogeneity; Deeks 2021). If the I^2 statistic was above 80%, we had planned to explore potential causes through sensitivity and subgroup analyses. However, none of our analyses demonstrated I^2 statistic > 80%. For future updates, if we cannot identify reasons for heterogeneity in subgroup or sensitivity analysis, we will not perform a meta-analysis but instead, provide outcome data for all studies without an overall effect estimate.

Assessment of reporting biases

As mentioned above, we searched trials registries to identify completed studies that have not been published elsewhere, to minimise or determine publication bias. We intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials (Sterne 2019). We considered $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in a meta-analysis. We performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We analysed studies that included different severities of disease separately, grouping them with respect to disease severity according to need for respiratory support at randomisation (see Types of outcome measures). We treated placebo and standard care as the same intervention, as well as standard care at different institutions and time points.

We used Review Manager Web (RevMan Web) software for analyses (RevMan Web 2019). One review author entered the data into RevMan Web, and a second review author checked the data for accuracy. We used the random-effects model for all analyses as we anticipated that true effects are related, but are not the same for included studies. If we deemed meta-analysis inappropriate for a certain outcome because of heterogeneity of included studies both statistically or conceptually or for too high a risk of bias, we presented descriptive statistics only.

If meta-analysis was possible, we assessed the effects of potential biases in sensitivity analyses (see Sensitivity analysis). For binary outcomes, we based the estimation of the between-study variance using the Mantel-Haenszel method. We planned to explore heterogeneity above 80% with subgroup analyses. If we could not find a cause for the heterogeneity, we did not perform a meta-analysis, but commented on the results as a narrative with the results from all studies presented in tables.

Subgroup analysis and investigation of heterogeneity

Because of clinical relevance, we performed subgroup analyses of mortality for the following characteristics, irrespective of observed statistical heterogeneity.

- Respiratory support at randomisation (for all comparisons planned, but currently possible only for the comparison of corticosteroids plus standard care versus standard care plus/minus placebo); respiratory support served as a baseline characteristic for the purpose of this analysis.
- Type of systemic corticosteroid (for the comparison of corticosteroids plus standard care versus standard care plus/minus placebo).

For future review updates, if the I^2 statistic is found to be above 80% for the other outcomes, we will also conduct subgroup analyses for these outcomes (see also Assessment of heterogeneity).

Sensitivity analysis

We performed the following sensitivity analysis for all outcomes:

- risk of bias assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias).

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the following outcomes, and prepared one summary of findings table per population.

Summary of findings

We used the GRADE pro GDT software to create summary of findings tables. For time-to-event outcomes, we would have calculated absolute effects at specific time points, as recommended in the GRADE guidance (Skoetz 2020).

According to Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions*, the "most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes" should be included in the summary of findings table(s) (Schünemann 2021). We included outcomes prioritised according to the core outcome sets for studies for the treatment of patients with confirmed or suspected COVID-19 (COMET 2020), and patient relevance. These outcomes were as follows.

Individuals with a suspected or confirmed diagnosis of COVID-19 and moderate to severe disease

- Mortality: all-cause mortality at day 14 or any longer observation period, in-hospital all-cause mortality
- Improvement of clinical status during the longest observation period available:
  - ventilator-free days
- Deterioration of clinical status during the longest observation period available:
  - new need for invasive mechanical ventilation, that is, transition to WHO 7 to 9 if 6 or lower at baseline (see Figure 1). If new need was not available directly, we used death as a proxy for assumed intubation counted together with patients alive and ventilated.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) during the longest period available
- Serious adverse events
- Adverse events (any grade)
- Hospital-acquired infections

Individuals with a suspected or confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- Mortality: all-cause mortality at day 14 or any longer observation period, in-hospital all-cause mortality
- Improvement of clinical status during the longest observation period available:
  - ventilator-free days
- Deterioration of clinical status during the longest observation period available:
  - new need for invasive mechanical ventilation, that is, transition to WHO 7 to 9 if 6 or lower at baseline (see Figure 1). If new need was not available directly, we used death as a proxy for assumed intubation counted together with patients alive and ventilated.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) during the longest period available
- Serious adverse events
- Adverse events (any grade)
- Infections

Assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the outcomes listed in the previous section.

The GRADE approach uses five domains (risk of bias, inconsistency, imprecision, indirectness and publication bias) to assess certainty in the body of evidence for each prioritised outcome.

We downgraded our certainty of evidence for:

- serious (-1) or very serious (-2) risk of bias;
- serious (-1) or very serious (-2) inconsistency;
- serious (-1) or very serious (-2) uncertainty about directness;
- serious (-1) or very serious (-2) imprecise or sparse data;
- serious (-1) or very serious (-2) probability of reporting bias.

The GRADE system used the following criteria for assigning grade of evidence.

- 'High': we are very confident that the true effect lies close to that of the estimate of the effect.
- 'Moderate': we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- 'Low': our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- 'Very low': we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 14 (Schünemann 2021).

We used the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. We phrased the findings and certainty in the evidence as suggested in the informative statement guidance (Santesso 2020).

Methods for future updates

Living systematic review considerations

Our information specialist (MIM) will provide us with new search records each week, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Living Evidence Network 2019).

We will manually check platform trials that were previously identified and listed as 'studies awaiting classification' for additional treatment arms.

We will wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We will consider one or more of the following components to inform this decision:

- findings of one or more prioritised outcomes;
- credibility (e.g. GRADE rating) of one or more prioritised outcomes;
- new settings, populations, interventions, comparisons or outcomes studied.

In case of emerging policy relevance because of global controversies around the intervention, we will consider republishing an updated review even though our conclusions remain unchanged. We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (for example, when additional comparisons, interventions, subgroups or outcomes, or new review methods become available).

RESULTS

Description of studies

Results of the search

We searched all databases and screened the resulting records up to 16 April 2021. We identified 1397 records. After removing duplicates, we screened 1246 records based on their titles and abstracts. We excluded 1131 records that did not meet the inclusion criteria. Of the remaining 115 records, we included 89 records:

- 11 RCTs (in 19 records) for inclusion in this review;
- 42 RCTs (in 51 records) are ongoing;
- 16 RCTs (in 19 records) are awaiting classification as they have been reported as being completed, but the results have not yet been published.

The study flow diagram in Figure 2 illustrates the study selection process according to PRISMA guidelines (Moher 2009).

Figure 2. PRISMA flow diagram illustrating our study selection process.

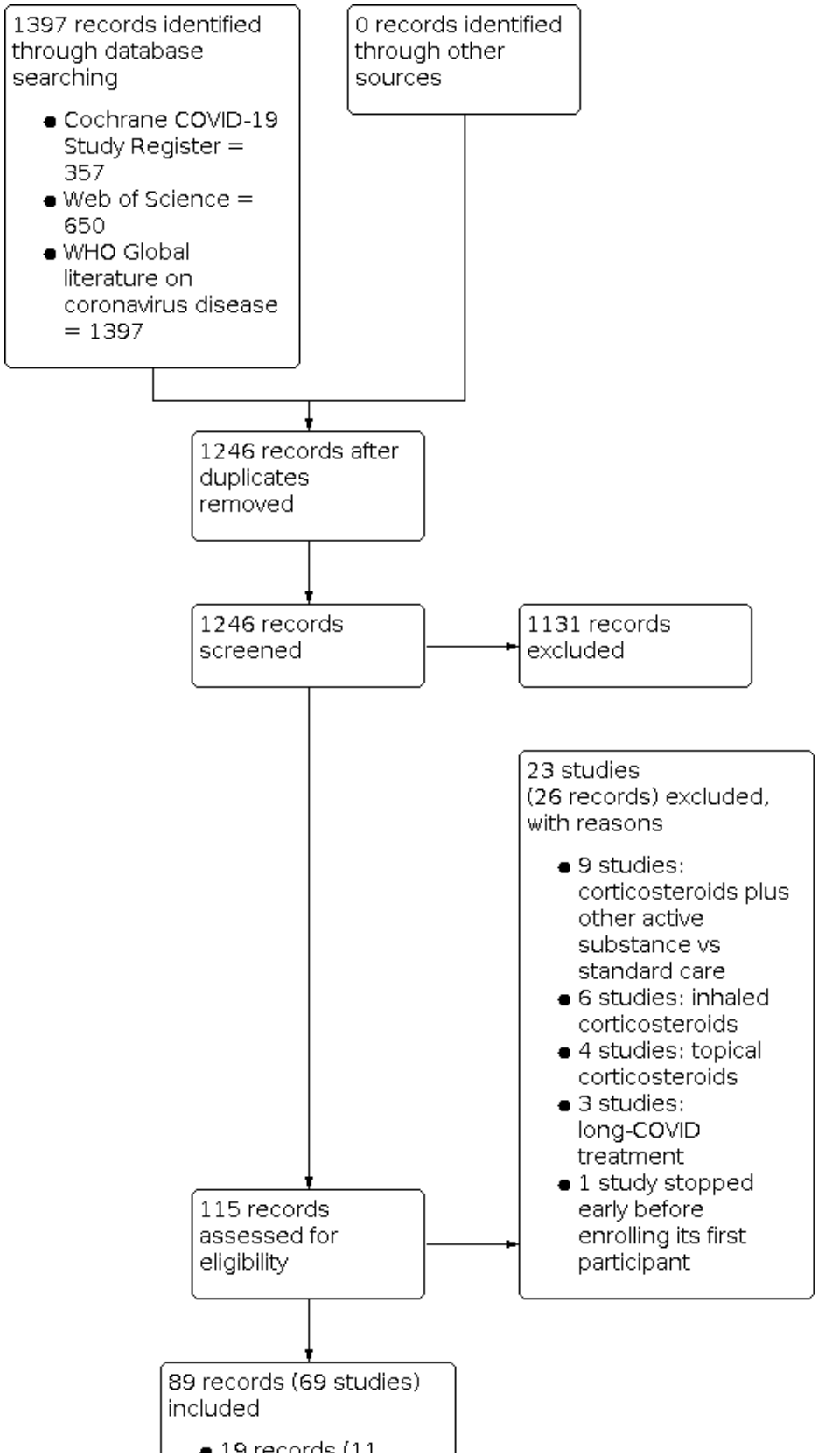
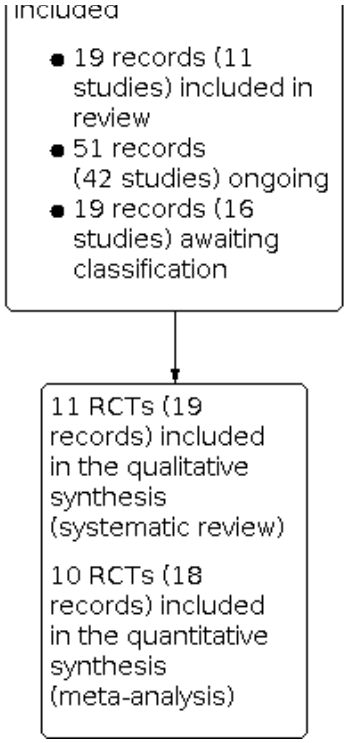


Figure 2. (Continued)



Included studies

Design and sample size

We included 11 studies, of which two were multi-centre platform RCTs (Horby 2021; Angus 2020), five were multi-centre RCTs (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), and four were single-centre RCTs (Farahani 2021; Jamaati 2021; Jeronimo 2020; Ranjbar 2021).

Setting

Of 8075 participants in the included studies, 7041 (87%) originated from high-income countries; there were no studies from low-income countries (World Bank Country Groups 2021). Seven studies originated from lower- and upper-middle-income countries (Edalatifard 2020; Farahani 2021; Jamaati 2021; Jeronimo 2020; Ranjbar 2021; Tang 2021; Tomazini 2020) and four from high-income countries (Angus 2020; Corral-Gudino 2021; Dequin 2020; Horby 2021).

Participants

All participants were adults hospitalised for either acute COVID-19 or, as in the case of Angus 2020, Dequin 2020, Horby 2021, Tomazini 2020 and Jeronimo 2020, suspected acute COVID-19. Positive RT-PCR rates within the studies ranged from about 95% in Dequin 2020 and Tomazini 2020 to about 80% in Angus 2020. All included participants were hospitalised because of symptomatic (suspected) COVID-19 and were treated with different levels of respiratory support (no oxygen, low-flow oxygen, high-flow oxygen or non-invasive ventilation, or invasive mechanical ventilation, including ECMO). Based on the different levels of respiratory support at baseline disease severity ranged from 4 to 9 on the WHO Clinical Progression Scale (Marshall 2020).

Interventions

All the completed studies included studies compared systemic corticosteroids, that is, hydrocortisone, prednisolone and methylprednisolone, and dexamethasone to standard care (plus/minus placebo), except one that compared methylprednisolone to dexamethasone (Ranjbar 2021). Daily hydrocortisone equivalents of the initial doses ranged from 150 mg to 5000 mg and durations of treatment ranged from zero to approximately 20 days. The majority of participants (n = 2561; 83%) randomised to corticosteroids received equivalents of 200 mg/day or less, 463 (15%) received 201 mg/day to 500 mg/day, and 48 (2%) received 501 mg/day to 5000 mg/day. The route of administration was intravenous except in Horby 2021, who allowed both oral and intravenous administration, and Farahani 2021, with oral dose-tapering after intravenous administration.

Included studies for comparison of corticosteroids plus standard care to standard care (plus/minus placebo)

We included 10 studies describing 7989 participants in this comparison, of whom 2986 were randomised to corticosteroids and 5003 to standard care (plus/minus placebo). Please see Table 1 for details, but note that no endpoint data from Farahani 2021 (29 participants) were applicable for further analysis, resulting in an analysis of nine trials only. Upon request, corresponding authors of three included studies provided us with additional data (Corral-Gudino 2021; Edalatifard 2020; Jeronimo 2020). They sent in all-cause mortality rates at the end of their respective observation periods stratified by respiratory support at randomisation. They also sent in definitions and rates of adverse events as well as rates of clinical improvement and deterioration based on new need for invasive ventilation on the one hand and weaning of initially invasively ventilated patients on the other.

Included studies for comparison of different types of systemic corticosteroids

We included Ranjbar 2021 describing 86 participants in this comparison, of whom 44 were randomised to methylprednisolone and 42 to dexamethasone. For details please see Table 2. The corresponding study author did not reply to our data request.

Outcome summary

In the setting of acute COVID-19 with immediate risk of death, we assumed in-hospital mortality and all-cause mortality with any observation period of 14 days and longer to be equivalent. The longest observation period was 60 days in Edalatifard 2020 and the shortest was 21 days in Dequin 2020, although most studies reported mortality at 28 days. All studies except Farahani 2021 reported utilisable dichotomous mortality data for 7930 participants overall in the comparison of corticosteroids versus standard care (plus/minus placebo) and 86 participants in the direct comparison of methylprednisolone and dexamethasone.

The reporting of adverse events, listed in Table 3, was heterogeneous among the 11 included studies. Only three studies explicitly reported adverse events regardless of their nature (Angus 2020; Edalatifard 2020; Tomazini 2020) for 618 participants. Another four studies reported specific adverse events related to the expected side effects of corticosteroids for 715 participants (Corral-Gudino 2021; Dequin 2020; Jeronimo 2020; Tang 2021).

Apart from that, one study with 6425 participants reported safety outcomes only for the intervention arm as suspected drug reactions (Horby 2021), and two studies with 79 participants did not report safety outcomes at all (Farahani 2021; Jamaati 2021).

Other efficacy outcomes were reported heterogeneously.

Ongoing studies

We identified 42 ongoing RCTs with systemic application of steroids for acute COVID-19 (details listed in Table 4), of which 30 were classified as 'recruiting' or 'ongoing' according to the study registrations. One was classified as 'temporarily halted'. Eleven were classified as 'not recruiting'. On excluding the studies that were not yet recruiting, the 31 studies that were recruiting, ongoing, and temporarily halted comprised a total of 10,083 expected participants. Most of the potentially eligible ongoing studies identified intend to recruit people who are admitted to hospital and require varying levels of respiratory support. Of the 42 ongoing studies, 16 planned to test dexamethasone, 14 methylprednisolone and three prednisolone. One study planned to compare different dexamethasone dosing regimens. Six studies planned to compare dexamethasone to methylprednisolone, and one study dexamethasone to prednisolone. One study planned to compare corticosteroids at different time points.

Studies awaiting classification

We identified 16 RCTs with systemic application of steroids for acute COVID-19 (details listed in Table 5). Of the 16 studies comprising 4036 expected participants, nine were classified as 'completed', three as 'prematurely ended', one as 'terminated (lack of enrolment)', one as 'terminated (too few patients)' and one terminated early (external evidence indicating benefit from corticosteroids in severe COVID-19), according to the study registrations. For one study, the preprint is available, but the methodology is unclear, so we are awaiting the publication of the full text. Three studies planned to compare dexamethasone, three methylprednisolone, two prednisolone, and one hydrocortisone or prednisone, to standard care or placebo. One study planned to compare different dexamethasone dosing regimens. Two studies planned to compare dexamethasone to methylprednisolone and one study dexamethasone to tocilizumab. Another study planned to compare dexamethasone plus hydroxychloroquine to hydroxychloroquine only. One study planned to compare methylprednisolone without specification of the control.

Excluded studies

We excluded 23 studies that did not meet our inclusion criteria.

- Nine studies investigated corticosteroids plus other active substances versus standard care (EUCTR2020-001445-39-ES; IRCT20120225009124N4; IRCT20190312043030N2; NCT04341038; NCT04411667; NCT04468646; NCT04561180; NCT04640168; NCT04826822);
- Six studies examined inhaled corticosteroids (EUCTR2020-001616-18-ES; EUCTR2020-001889-10; ISRCTN86534580; NCT04355637; NCT04381364; NCT04416399);
- Four studies investigated topical corticosteroids (IRCT20200522047542N1; NCT04361474; NCT04484493; NCT04569825);
- Three studies considered corticosteroids for long-COVID treatment (NCT04551781; NCT04534478; NCT04657484);
- One study stopped early before enrolling its first participant (NCT04359511).

Risk of bias in included studies

We assessed the risk of bias of results from 10 RCTs that contributed to our analyses (Angus 2020; Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Horby 2021; Jamaati 2021; Jeronimo 2020; Ranjbar 2021; Tang 2021; Tomazini 2020), using the RoB 2 tool (version 22 August 2019) recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b). We made no assessment of bias for Farahani 2021 as it did not report any outcomes relevant to this review.

The completed RoB 2 tool with responses to all assessed signalling questions is available online at: https://zenodo.org/record/5155770.

Overall judgements for studies that included hospitalised individuals with a confirmed or suspected diagnosis of symptomatic COVID-19

All-cause mortality

We assessed this outcome on a study level at days 21, 28 and 60. Among the studies that reported this outcome, we considered the risk of bias to be of some concern for nine studies (Angus 2020; Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Horby 2021; Jamaati 2021; Jeronimo 2020; Ranjbar 2021; Tomazini 2020). In Tomazini 2020 (9.4 % of the participants in the control group received corticosteroids), Horby 2021 (8% of the participants in the control group received corticosteroids) and Edalatifard 2020 (17% of the participants in the control group

received corticosteroids) there were deviations from the intended intervention. In Jamaati 2021, no study protocol or analysis plan was available and baseline differences between intervention groups raised some concerns for the risk of bias. Dequin 2020 reported mortality as a post-hoc outcome, raising some concerns for risk of bias. Corral-Gudino 2021 had different definitions of mortality in the trials register and the actual study. In Jeronimo 2020 participants were excluded from the study and from the analysis. We assessed Angus 2020 to be of some concerns because of deviations from the intended intervention (15% of the participants in the no-hydrocortisone group received hydrocortisone) and differences in standard care given at the various hospitals.

Other outcomes

After planning the analysis and sending data requests to the corresponding authors we became increasingly aware of possible confounding through a competing risk of death in the following exploratory outcomes. The way we addressed the issue is explained in Quality of the evidence but we have also elaborated below wherever applicable.

Clinical improvement: liberation from invasive mechanical ventilation

Apart from Tomazini 2020, no study reported this outcome, so we requested the missing data from the study authors. For both Tomazini 2020 and the studies for which we received data (Corral-Gudino 2021; Edalatifard 2020; Jeronimo 2020), we considered the risk of bias to be high because there could be relevant confounding through death as a competing risk in this analysis if no adjustment is done. We discuss this issue in Quality of the evidence.

Clinical improvement: ventilator-free days

One study reported ventilator-free days (Tomazini 2020). We rated the risk of bias for Tomazini 2020 to be of some concern because some participants in the control group received corticosteroids and these deviations from the intended intervention were not balanced between the two study arms. Conceptual limitations peculiar to this endpoint are discussed in Quality of the evidence.

Clinical deterioration: new need for invasive mechanical ventilation

Apart from Jamaati 2021 and Tomazini 2020, no other studies reported this outcome, so we requested missing data from the study authors. Among the studies for which we received data (Corral-Gudino 2021; Edalatifard 2020; Jeronimo 2020) and for Jamaati 2021 and Tomazini 2020 as well, we considered the risk of bias to be high because there could be relevant confounding through death as a competing risk in this analysis if no adjustment is done.

Clinical deterioration: need for dialysis

Two studies reported this outcome (Horby 2021; Jeronimo 2020). We considered the risk of bias to be high because there could be relevant confounding through death as a competing risk in this analysis if no adjustment is performed.

Quality of life

We could not assess risk of bias for this outcome, because none of the included studies reported quality of life or neurological long-term outcome.

Viral clearance

Jeronimo 2020 reported this outcome, which we rated high risk of bias because there could be relevant confounding through death as a competing risk in this analysis if no adjustment is done.

Serious adverse events

Two studies reported this outcome for 678 participants (Angus 2020; Tomazini 2020). Overall, we considered the risk of bias, among those studies having reported adverse events, to be high, mainly because there could be relevant confounding through death as a competing risk in this analysis if no adjustment is done.

Adverse events

Five studies reported this outcome for 660 participants (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020). Overall, we considered the risk of bias to be high for all five studies. The definition of adverse events was heterogeneous as described in Table 3 and there could be relevant confounding through death as a competing risk in this analysis if no adjustment is performed.

Hospital-acquired infections

Five studies reported this outcome in 660 participants (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020). Overall, we considered the risk of bias to be high for all five studies mainly because there could be relevant confounding through death as a competing risk in this analysis if no adjustment is done.

Effects of interventions

See: **Summary of findings 1** Summary of Findings Table - Systemic corticosteroids plus standard care compared to standard care for adults with a suspected or confirmed diagnosis of COVID-19; **Summary of findings 2** Summary of Findings Table - Methylprednisolone compared to dexamethasone for adults with a suspected or confirmed diagnosis of COVID-19

Hospitalised individuals with a confirmed or suspected diagnosis of symptomatic COVID-19

From 11 RCTs in this population (Angus 2020; Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Farahani 2021; Horby 2021; Jamaati 2021; Jeronimo 2020; Ranjbar 2021; Tang 2021; Tomazini 2020), Farahani 2021 did not report any of the prioritised outcomes of interest.

Systemic corticosteroids plus standard care versus standard care (plus/minus placebo)

The evidence profile is presented in Summary of findings 1.

All-cause mortality at day 14 or any longer observation period

Data on all-cause mortality were available from nine studies with a total of 7930 participants (Angus 2020; Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Horby 2021; Jamaati 2021; Jeronimo 2020; Tang 2021; Tomazini 2020). Edalatifard 2020, which involved 60 participants, did not report the follow-up time of mortality, but we found out through our author enquiry that it was 60 days. Thus, observation periods ranged from 21 to 60 days, with most studies reporting 28-day mortality. Overall, 760 of 2955 participants in the intervention group died compared with 1367 of 4975 participants

in the control group. The RR of death was 0.89 (95% CI 0.80 to 1.00; I^2 = 10%; random-effects model; Analysis 1.1). We downgraded the certainty of evidence for this outcome from high to moderate due to the risk of bias.

Subgroup analyses

- **Respiratory support at randomisation:** we are unable to rule out differences in the effect of corticosteroids on mortality between different levels of baseline respiratory support (P = 0.08; Analysis 2.1). In contrast with the beneficial effect on mortality in all other subgroups needing respiratory support, a higher risk of death with corticosteroids was seen among symptomatic COVID-19 participants who did not need any respiratory support (RR 1.27, 95% CI 1.0 to 1.61). The analysis of participants without respiratory support was from a single study (Horby 2021).
- **Dexamethasone versus methylprednisolone versus hydrocortisone indirectly compared for their effect relative to placebo/standard care:** the test for subgroup differences indicated no difference (P = 0.48) between subgroups stratified by type of systemic corticosteroid (Analysis 3.1). However, the effect estimates for each agent's subgroup were in favour of corticosteroid use.

The power to detect differences in both subgroup analyses was limited.

Sensitivity analyses

We could not perform any of our planned sensitivity analyses for the comparison of systemic corticosteroids plus standard care versus standard care (plus/minus placebo) and the outcome of all-cause mortality.

Clinical improvement: liberation from invasive mechanical ventilation

Data on liberation from invasive mechanical ventilation can be taken from Analysis 1.2. We decided not to carry out a meta-analysis because we are highly uncertain about the size and direction of the unadjusted effects.

Clinical improvement: ventilator-free days

One study with 299 participants reported ventilator-free days (Tomazini 2020). The mean difference was 2.6 days (95% CI 0.67 to 4.53; Analysis 1.3). We downgraded the certainty of the evidence from high to low. The limitations of the endpoint are discussed in Quality of the evidence.

Clinical deterioration: new need for invasive mechanical ventilation

Data on the new need for invasive mechanical ventilation can be taken from Analysis 1.4. We decided not to carry out meta-analysis because we are highly uncertain about the size and direction of the unadjusted effects.

Clinical deterioration: need for dialysis

Data on the need for dialysis can be taken from Analysis 1.8. We decided not to carry out meta-analysis because we are highly uncertain about the size and direction of the unadjusted effects.

Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available

Data on quality of life were not available in any study.

Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3 and 7 days

Data on viral clearance can be taken from Analysis 1.9. We decided not to carry out meta-analysis because we are highly uncertain about the size and direction of the unadjusted effects.

Serious adverse events

Two studies reported serious adverse events for 678 participants. Data on serious adverse events can be taken from Analysis 1.5. We decided not to carry out a meta-analysis because we are highly uncertain about the size and direction of the unadjusted effects. However, a cautious analysis of the descriptive statistics suggested little to no difference between the groups.

Adverse events (any grade)

Five studies reported adverse events for 660 participants with four studies focussing on a limited set of adverse events only (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021). Data on adverse events can be taken from Analysis 1.6. We decided not to carry out meta-analysis because we are highly uncertain about size and the direction of the unadjusted effects. However, a cautious analysis of the descriptive statistics suggests little to no difference between the groups.

Hospital-acquired infections

Five studies reported hospital-acquired infections for 660 participants. Data on hospital-acquired infections can be taken from Analysis 1.7. We decided not to carry out meta-analysis because we are highly uncertain about size and the direction of the unadjusted effects. However, a cautious analysis of the descriptive statistics suggests little to no difference between the groups.

Different types of systemic corticosteroids: methylprednisolone versus dexamethasone

The evidence profile is presented in Summary of findings 2.

All-cause mortality at day 14 or any longer observation period

Data on all-cause mortality at 28 days was available for one trial with 86 participants (Ranjbar 2021). Eight of 44 participants in the intervention group died compared with 15 of 42 participants in the control group. The RR of death was 0.51 (95% CI 0.24 to 1.07; Analysis 4.1). We downgraded the certainty of the evidence for this outcome to very low due to risk of bias and very serious imprecision.

Subgroup analyses

We could not perform any of our planned subgroup analyses for the comparison of methylprednisolone versus dexamethasone and the outcome of all-cause mortality.

Sensitivity analyses

We could not perform any of our planned sensitivity analyses for the comparison of methylprednisolone versus dexamethasone and the outcome of all-cause mortality.

Clinical improvement: liberation from invasive mechanical ventilation

We did not identify any study reporting this outcome and also received no response to our author request.

Clinical improvement: ventilator-free days

We did not identify any study reporting this outcome.

Clinical deterioration: new need for invasive mechanical ventilation

Data on new need for invasive mechanical ventilation can be taken from Analysis 4.2. We decided not to carry out a meta-analysis because we are highly uncertain about the size and direction of the unadjusted effects.

Clinical deterioration: need for dialysis

We did not identify any study reporting this outcome.

Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available

We did not identify any study reporting this outcome.

Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days

We did not identify any study reporting this outcome.

Serious adverse events

We did not identify any study reporting this outcome.

Adverse events (any grade)

We did not identify any study reporting this outcome.

Hospital-acquired infections

We did not identify any study reporting this outcome.

Dose comparisons

No studies provided data for this comparison.

Timing comparisons (early versus late)

No studies provided data for this comparison.

Systemic corticosteroids versus other active substances

No studies provided data for this comparison.

Outpatients with asymptomatic or mild disease

We did not identify any study that investigated the effects of systemic corticosteroids in people with asymptomatic infection or mild disease (i.e. non-hospitalised individuals).

DISCUSSION

Summary of main results

This review aimed to assess the efficacy and safety of systemic corticosteroids for the treatment of COVID-19. We identified 11 RCTs (Angus 2020; Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Farahani 2021; Horby 2021; Jamaati 2021; Jeronimo 2020; Ranjbar 2021; Tang 2021; Tomazini 2020). The studies evaluated 8075 participants, of whom 3072 received corticosteroids. We identified 42 ongoing studies evaluating systemic corticosteroids and 16 completed studies lacking published results that we categorised as 'studies awaiting classification'. We checked the proportion of PCR-positive tests in each study, as some studies included confirmed or suspected COVID-19 infections, or both. The studies with the lowest PCR-positive rate of approximately 80% were Angus 2020 and Jeronimo 2020.

Effects of interventions

Hospitalised individuals with a confirmed or suspected diagnosis of symptomatic COVID-19

A total of 10 RCTs (8075 participants) evaluated systemic corticosteroids amongst hospitalised individuals: nine RCTs (7989 participants) compared corticosteroids plus standard care to standard care (plus/minus placebo), and one RCT (86 participants) compared methylprednisolone to dexamethasone.

Systemic corticosteroids plus standard care versus standard care (plus/minus placebo)

Systemic corticosteroids probably slightly decrease all-cause mortality in hospitalised people with COVID 19. Based on the observed rate of 275 deaths per 1000 in the control arms, treatment with corticosteroids led to 30 fewer deaths (moderate-certainty evidence). To further explore differences in the effect of systemic corticosteroids depending on the severity of COVID-19, we performed a subgroup analysis stratified by respiratory support at randomisation, since respiratory support can be seen as a strong indicator for disease severity. Although there was no statistically significant subgroup difference, evidence of a negative effect on mortality has to be noted in the participants without respiratory support.

In addition to the slight reduction in mortality, as a further beneficial effect, corticosteroids may increase the composite outcome of ventilator-free days (MD 2.6 days more than in the control arm with 4 days), although certain limitations of the endpoint need to be considered (see Quality of the evidence). Further outcomes in which risk of bias assessment led to the decision not to perform meta-analysis were the need for dialysis, need for invasive ventilation, liberation from invasive ventilation, and viral clearance. Nonetheless, a cautious analysis of descriptive statistics might render the interpretation that there is no evidence to suspect further relevant effects on these outcomes for people with COVID-19 treated with systemic corticosteroids.

Since all studies besides Tomazini 2020, among them the largest study, Horby 2021, did not report safety data (namely serious adverse events, adverse events, and hospital-acquired infections) in detail, we see a relevant underreporting of these important parameters to characterise the safety profile of systemic corticosteroids for the treatment of COVID-19. Due mainly to a high risk of bias and heterogeneous reporting, we deemed quantitative synthesis inappropriate. Nonetheless, an analysis of the descriptive statistics of the included studies did not generate suspicion of an exceedingly large harmful effect of systemic corticosteroid treatment.

Different types of systemic corticosteroids: methylprednisolone versus dexamethasone

We are uncertain whether methylprednisolone decreases all-cause mortality directly compared to dexamethasone (1 RCT, 86 participants, very low-certainty evidence).

Different dosages or timing of systemic corticosteroids

None of the included studies provided data on different dosages or timing.

Outpatients with asymptomatic or mild disease

Currently, there are no studies published in populations with asymptomatic infections or mild disease.

Overall completeness and applicability of evidence

Diagnosis of COVID-19 was confirmed by positive SARS-CoV-2 PCR testing in 93.8% of the participants. In terms of virological aspects all participants included in this review were evaluated during the first months of the pandemic. Our findings might not apply to a different pathogenicity of later variants of SARS-CoV-2. The majority of participants also received various COVID-19 treatment options such as antibiotics with potential antiviral and anti-inflammatory properties (i.e. azithromycin), hydroxychloroquine, convalescent plasma, or combinations of these drugs. None of the trials evaluated participants with asymptomatic infections or mild disease (non-hospitalised participants).

The study participants were mainly from high-income countries. Only 13% of participants came from middle-income countries and none from low-income countries. This finding is even more important as the proportion of severe COVID-19 cases can be expected to further decrease in high-income countries with successful vaccination programmes in place in many of them. Thus, the evidence presented in this review might only partially apply to people with COVID-19 who are treated under different circumstances to those of most studies included in our review. In low- and middle-income countries, there might be a more severe shortage of hospital beds in both ordinary wards and intensive care units, shortage of oxygen and other resource constraints on the delivery of respiratory support, and other aspects of care labelled as standard care in this review.

In terms of the types of systemic corticosteroids, our included RCTs evaluated dexamethasone, methylprednisolone, and hydrocortisone. With the exception of Edalatifard 2020 , the dosages of corticosteroids in the RCTs included for the comparison of systemic corticosteroids versus standard care only were significantly lower, (i.e. ≤ 500 mg/day hydrocortisone equivalent) than the usual immunosuppressive dosage of more than 1250 mg/day hydrocortisone equivalent (Angus 2020; Corral-Gudino 2021; Dequin 2020; Horby 2021; Jamaati 2021; Jeronimo 2020; Tang 2021; Tomazini 2020). The only study with high-dose corticosteroids was Edalatifard 2020 (1250 mg/day hydrocortisone equivalent). We have not explored in a subgroup analysis a possible different effect of relatively low-dose strategies (≤ 500 mg/day hydrocortisone equivalent) compared to those commonly referred to as short-term, high-dose, 'pulse' regimens (> 1250 mg/day) because we had not planned it and because there were too few data for the latter. As part of our living review approach, we plan to address these knowledge gaps in subsequent updates of this review.

Different scales of disease severity and progression were used across studies, and the terms 'mild', 'moderate', 'severe', and 'critical' have been inconsistently used in the different guidelines and consensus statements of national and international organisations (Marshall 2020; WHO Living Guidance 2021). Hence, we decided to use the need for respiratory support (no oxygen, low-flow oxygen support, non-invasive ventilation/high-flow nasal cannula, and invasive ventilation) at randomisation and its changes as a surrogate for COVID-19 disease severity. For hospitalised patients, the need for respiratory support is a strong predictor of mortality, essentially determines the pathway within the hospital (e.g. ICU admission), and, from the individual patient's perspective, has a strong impact on acute health-related quality of life, functional independence, and autonomy. We deem respiratory support at randomisation both a good indicator for disease severity and a surrogate for the timing of intervention. Among the 7818 participants for whom we could extract respiratory support at randomisation, the distribution was as follows: for the comparison of corticosteroids in addition to standard care and standard care only, 1560 participants (20%) did not receive any additional oxygen, 4489 (57%) received any non-invasive respiratory support (oxygen prongs or mask, high-flow nasal cannula, or non-invasive ventilation), and 1769 (23%) received invasive ventilation at randomisation. For the comparison of two different types of corticosteroids, we identified one study (Ranjbar 2021). In this study, the participants probably received non-invasive respiratory support (low-flow oxygen, high-flow nasal cannula, or non-invasive ventilation) at randomisation.

We also note the lack of safety data (serious adverse events, adverse events, and hospital-acquired infections) reported by included studies: only two evaluated serious adverse events for 678 participants, five reported partly selected adverse events for 660 participants, and five studies provided information on hospital-acquired infections for 660 participants.

With regard to additional evidence from future publications, there are 31 ongoing, recruiting or temporarily halted studies encompassing approximately 10,000 participants, and 16 studies described as completed, prematurely ended, or terminated encompassing approximately 4000 participants. Most of the studies intend to recruit people treated with different levels of respiratory support. With the publication of even parts of these data, possible publication bias would be countered and changes to the precision and effect estimates themselves are not unlikely, although we do not expect a relevant difference or even change of direction in the effect of mortality in the first comparison but rather more precise estimates for subgroup analyses and the subordinate outcomes.

Quality of the evidence

Systemic corticosteroids plus standard care versus standard care (plus/minus placebo)

We included data from nine RCTs into the analysis of efficacy and safety of systemic corticosteroids. The population of interest was hospitalised individuals with a confirmed or suspected diagnosis of symptomatic COVID-19 when compared to treatment with standard care (plus/minus placebo).

We had moderate to very low certainty in the identified evidence.

- All-cause mortality: we downgraded for risk of bias for deviation from intended interventions (Angus 2020; Edalatifard 2020; Horby 2021; Jeronimo 2020; Tomazini 2020), for selective reporting (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Jamaati 2021), for missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), for baseline differences (Jamaati 2021) and indirectness (mortality observed at 21 to 60 days; in most studies 'at 28 days' should be seen as a proxy for long-term survival as long as we are unsure about its predictive value; 1 point altogether).

- Ventilator-free days: we downgraded for risk of bias through deviation from intended interventions (Tomazini 2020; 1 point), and imprecision (broad confidence interval, low number of evaluated participants; 1 point).
- New need for invasive ventilation: we downgraded because of risk of bias mainly for problems with deviations from intended interventions (Edalatifard 2020; Jeronimo 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), baseline differences (Jamaati 2021), missing pre-specification (Corral-Gudino 2021; Edalatifard 2020; Jamaati 2021; Jeronimo 2020), missing adjustment for competing risk (the term is discussed below in detail) (Corral-Gudino 2021; Edalatifard 2020; Jamaati 2021; Jeronimo 2020; 2 points), and imprecision (fewer than 500 events; 1 point).
- Serious adverse events: we downgraded for risk of bias for deviations from intended interventions (Angus 2020; Tomazini 2020), missing adjustment for competing risk (Angus 2020; Tomazini 2020; 2 points), publication bias because 2 out 10 studies including the largest, Horby 2021, did not report this major safety outcome (downgraded 1 point), and imprecision (fewer than 500 events; 1 point).
- Adverse events: we downgraded because of risk of bias mainly through deviation from intended intervention (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), and selection of adverse events usually associated with corticosteroids (Corral-Gudino 2021; Edalatifard 2020; Tang 2021; 2 points), imprecision (fewer than 500 events; 1 point), and publication bias (only 5 out of 10 studies reported this established safety outcome; 1 point)
- Hospital-acquired infections: we downgraded because of risk of bias mainly from deviation from intended interventions (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), missing pre-specification of its definition (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; 2 points), imprecision (fewer than 500 events; 1 point), and publication bias (only 5 out of 10 studies reported this outcome, which represents an adverse event; 1 point).

Comparison of different types of corticosteroids

Methylprednisolone versus dexamethasone

We included the data from one RCT assessing the efficacy and safety of methylprednisolone for individuals with a confirmed or suspected diagnosis of COVID-19 when compared to treatment with dexamethasone.

We had low to very low certainty in the identified evidence.

- All-cause mortality at 28 days: we downgraded to very low certainty due to risk of bias based on missing pre-specification/protocol/statistical analysis plan (1 point), and serious imprecision (fewer than 50 events; 2 points).
- New need for invasive ventilation: we downgraded to very low certainty due to risk of bias based on missing data/adjustment for competing risk and missing protocol/statistical analysis plan (1 point), and serious imprecision (fewer than 50 events; 2 points).

Critical appraisal of selected outcome parameters

Outcomes with death as competing risk

Death and our exploratory endpoints in the domain of clinical improvement and deterioration, as well as safety data, have to be seen as semi-competing risks for each other: death precludes the occurrence of non-terminal outcomes if participants die early. Consequently, the analysis of mortality using dichotomous, metric or time-to-event data is unaffected by this and is thus considered robust in general.

However, any non-terminal event like the need for invasive ventilation, liberation from invasive ventilation, or even occurrence of adverse events can be severely skewed by different counts and time points of deaths in each arm. This can be illustrated with a theoretical example: if, because of a hypothetical pathophysiologic mechanism or even chance, participants in the intervention arm tend to live 10 days longer on average during an observation period of 28 days, their chance of experiencing an adverse event might be higher than in the control arm, even though death counts are equal or even lower in the intervention arm at the end of the observation period. This leads to the conclusion that a simple analysis of endpoints representing non-terminal events regardless of the scale level might be misleading.

An inappropriate solution to this would be the exclusion of those with terminal events from the analysis because it creates new, non-randomised samples. Likewise, in continuous outcomes, where assigning any values to those with terminal events implies the relative grading of different outcomes, representing an ethical or even economical weighting rather than a mathematically valid adjustment. In this instance, composite endpoints are often used as a compromise to both increase statistical power and address the issue of competing risks. Nonetheless, they have relevant methodological limitations mainly with regard to the possible asymmetry of the effect-driving component in the treatment arms and the hierarchy of the components. We elaborate on that at the end of this section on the basis of our endpoint ventilator-free days.

In order to obtain a statistically correct and practically helpful analysis of the described multi-state model (e.g. death as a terminal state and adverse events or clinical deterioration or improvement as non-terminal states), individual data for each study participant and each event posing competing risks as well as methodology beyond the means of the first publication of this living review would be required (Columbia Public Health 2021, Wu 2020, Brock 2011).

We addressed competing risks as an issue of bias in Domain 3 as described in the detailed ROB 2 guidance (Higgins 2019). This led to all outcomes except mortality and ventilator-free days being assessed as having a high risk of bias. This is because measuring the respective non-terminal outcomes on a dichotomous or even simple metric scale and without proper adjustment for competing risks can be seen as an inappropriate measurement due to missing data. Second, we decided not to perform any meta-analysis or synthesis without meta-analysis (SwiM) for those outcomes affected because we are uncertain as to not only the size but also the direction of the unadjusted effects. We only presented the raw numbers as extracted or sent in by the authors (Analysis 1.2; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7;

Analysis 1.8; Analysis 1.9; Analysis 4.2). Finally, we would like to emphasise that, in doing so, it is our intention to make transparent our ongoing internal discussion on biostatistical aspects of the proposed Core Outcome Set for COVID-19 (Tong 2020), which we initially adopted for our protocol. The aforementioned detailed individual time-to-event data have not yet been requested from the authors. Alternatively, data already adjusted by the study authors themselves could be presented.

Ventilator-free days and other composite outcomes

Ventilator-free days and a range of other composite endpoints come with a conceptual peculiarity: depending on the metric value that is assigned to deceased participants (e.g. zero days), they are more robust against competing risk of death than other common endpoints (e.g. simple duration of ventilation) but offer only a rather abstract measure of disease severity. Therefore, a meta-analysis of ventilator-free days is downgraded for imprecision due to different underlying definitions and even more difficult to interpret from the patient or economical perspective. Depending on the respective definition and distribution in the study arms, there can be an unintended mismatch in how the individual components (death, supposedly more important, and ventilation duration, supposedly less important) drive the effect of the composite outcome. Therefore, even if ventilator-free days as a composite endpoint is more robust against competing risks, a meta-analysis of the ventilator-free days should thoroughly compare and evaluate the distribution of the individual components in the different study arms, consider hidden competing risks for ventilator-free days, and might be paralleled by a competing risk regression analysis or similar procedures. Moreover, it should be plausible that both components are affected in the same direction. But, most importantly, authors should state why they chose ventilator-free days, or any other composite outcome, to primarily measure the efficacy of a drug if in a disease death itself occurs at a sufficiently high rate to detect differences if they were relevant (Yehya 2019). Tackling these issues in detail was beyond the scope of the methodology of this first version of the review.

Potential biases in the review process

In addition to peer-reviewed, full-text articles, we also included preprints. We are aware of the potentially lower quality of preprint publications, and that results could change once the peer-reviewed journal publications are available. In cases of missing data, we contacted study authors for additional data or relevant details if we needed more information. We are confident that we identified all relevant studies and will monitor ongoing studies as well as full publications of preprints closely after the publication of this review.

Agreements and disagreements with other studies or reviews

Here, we discuss four important systematic reviews with meta-analyses including only RCTs.

First, the systematic review by Pasin 2021 had a design very similar to ours. Their analysis of mortality included 7692 participants from five RCTs with a pooled effect size and precision similar to ours. Our analysis included four further RCTs (Corral-Gudino 2021; Edalatifard 2020; Jamaati 2021; Tang 2021), and final data from Jeronimo 2020, which had not been fully published at the time of their latest search date. Additionally, our subgroup analysis of mortality stratified by the need for respiratory support contains intermediary levels and more participants because of the aforementioned additional publications and requests to authors. As we used similar methods, the two reviews share limitations except for a smaller publication bias in our case. Nevertheless, their conclusion of a probable positive effect on mortality carried by a stronger effect among invasively ventilated participants, and even a negative effect among the moderately ill, is similar to ours.

Second, Sterne 2020 published a prospective systematic review searching three major study registries. They focussed on critically ill patients and their analysis of mortality included 1703 participants from seven RCTs with a pooled effect and precision similar to our subgroup result of invasively ventilated participants (random-effects odds ratio (OR) 0.70 (95% CI 0.48 to 1.01)). They partly included data of trials not completed at that time, and three of the included trials have not yet published their data yet, so we could not include them at this stage. Owing to the review design and consequent homogeneity of the study populations and settings, analysis conducted by Sterne 2020 might be more robust than ours, but it did not encompass trials registered in other registries, and their last day of follow-up on 6 July 2020 is almost one year ago now. Moreover, their chosen effect measure, that is, odds ratio, exaggerates effects when the number of participants with events is large — as in the population examined here — compared to the risk ratio we present (Ranganathan 2015). Nonetheless, the conclusion of a probable positive effect on 28-day all-cause mortality in participants with severe disease is similar to ours.

Third, Chaudhuri 2021 conducted a systematic review and focussed on invasively ventilated patients with ARDS, both with and without COVID-19. Excluding the non-COVID-19-related data as indirect evidence, their meta-analysis of mortality data included 1741 participants, quasi-resembling Sterne 2020 , with the last search date of 6 September 2020, including partially unpublished data or preprints as well. They found little to no evidence of a slight beneficial effect on mortality in the above-specified subgroups.

Fourth, the living systematic review with network meta-analysis by Siemieniuk 2020 included published and unpublished data on 2975 participants who received corticosteroids (latest update on 6 April 2021), comparable to the 2955 participants in this review regarding the all-cause mortality analysis. They found a probable slight beneficial effect (random-effects model OR 0.83, 95% CI 0.69 to 0.98) with moderate certainty; this is in line with our findings but with the aforementioned limitation of the effect measure. Their result for ventilator-free days also compares well to ours.

Of note, the above-listed systematic reviews performed meta-analyses to various extents for endpoints that we deemed to be at risk of bias too high for quantitative synthesis. Therefore, we decided not to repeat their findings but state that we consider none of these endpoints to be relevant in terms of effect size and quality of the evidence to remarkably change the view on corticosteroids in COVID-19. We also decided not to further discuss systematic reviews that included observational data while comprehensive RCT-only systematic reviews are available. Nonetheless, we would like to name Van Paassen 2020 as an example of how trialists worldwide contributed to the search for evidence in the initial phases of the pandemic.

Finally, the single study Horby 2021 must be discussed due to its huge impact. Not only was it the largest contributor to

our review in terms of events and participants, it also had an immense influence on treatment guidelines and ongoing studies in 2020 (WHO Living Guideline 2021). The reported direction of the effect on mortality is congruent to our findings as well as the findings in the subgroup analysis stratified by respiratory support at randomisation. However, we observed smaller effects with similar precision after the inclusion of eight further RCTs. Without a doubt, platform trials like this one offer great chances for rapid and adaptive generation of evidence involving huge numbers of participants in the pandemic. Nevertheless, systematic appraisal of their specific sources of risk of bias is critical but not yet well-established and beyond the scope of this first version of this living review (Park 2020).

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current evidence, we are moderately certain that systemic corticosteroids probably reduce mortality slightly amongst hospitalised, symptomatic COVID-19 patients. Most of the participants in the studies were treated with invasive mechanical ventilation and non-invasive ventilation/continuous positive airway pressure or high-flow oxygen. In a subgroup analysis by baseline respiratory support, evidence of an increased risk of mortality with corticosteroids in symptomatic, hospitalised COVID-19 patients without any need for additional oxygen, was limited by a lack of statistical significance. In a subgroup analysis of different types of systemic corticosteroids on mortality, we did not identify evidence for a subgroup difference.

There is low-certainty evidence for a beneficial effect of corticosteroids in the observed reduction of ventilator-free days; however, the current evidence remains uncertain due to methodological limitations.

There is very low certainty direct evidence for the comparison of methylprednisolone versus dexamethasone, results remain uncertain.

Due to the underreporting of relevant data, we have very low certainty about the safety of systemic corticosteroids as treatments for COVID-19.

We did not identify any published study to evaluate different dosages or timing of corticosteroids in hospitalised participants. Currently, there is no evidence to characterise the benefits and harms of corticosteroids in patients with asymptomatic or mild disease (non-hospitalised).

Implications for research

There is an urgent need for long-term data on survival and patient-centred outcomes like quality of life, neurological function and independence in daily activities. To improve patient selection for treatment, good-quality evidence is needed for specific subgroups of disease severity, for which we propose definition by level of respiratory support at randomisation. This also applies to the subgroups of different types and doses of corticosteroids. Outcomes apart from mortality should be measured and analysed appropriately, accounting for the competing risk of death. Furthermore, the existing datasets of the included studies should re-analysed by the study authors to gain more information about the safety profile of corticosteroids in COVID-19 patients with different disease severity, age, and co-morbidities. The data are urgently needed by physicians and their patients to weigh up the benefits and harms of treating COVID-19 with systemic corticosteroids in a more patient-adapted, individualised way.

As we could not identify published RCTs on non-hospitalised patients with mild or asymptomatic disease treated with systemic corticosteroids, strong efforts should be made to collect good-quality data regarding these patients.

We identified 42 ongoing and 16 completed but unpublished RCTs in trials registries, which will probably increase the certainty of the evidence in the future. The studies mainly intend to recruit people with severe disease who require respiratory support. In accordance with the living approach of this review, we will continually update our search and include eligible trials.

ACKNOWLEDGEMENTS

ALF, FF, MG, and KK are thankful for the support of their colleagues with the Department of Anesthesia and Intensive Care at the University of Leipzig Medical Center while working on the manuscript of this review during the COVID-19 pandemic.

We thank the investigators of three studies for providing us with additional information and data (Corral-Gudino 2021; Edalatifard 2020; Jeronimo 2020). We also thank the investigators of the platform trials Angus 2020 and Horby 2021 with whom the data sharing is in progress.

Cochrane Haematology supported the authors in the development of the protocol and review. Cochrane's Central Editorial Service (https://community.cochrane.org/review-production/production-resources/cochranes-central-editorial-service) conducted the editorial and peer-review process for this article. Contributors to the editorial process were: Toby Lasserson, Sign-off Editor (final editorial decision), Cochrane's Editorial and Methods Department; Joey Kwong, Managing Editor (selecting peer reviewers, collating peer-reviewer comments, providing editorial guidance to authors, editing), Cochrane's Editorial and Methods Department; Leticia Rodrigues, Editorial Assistant (editorial policy checks and supporting editorial team), Cochrane's Editorial and Methods Department; Denise Mitchell, Copy Editor (copy-editing and production), Cochrane's Editorial and Methods Department. Peer-reviewers (providing comments and a recommendation) were: Nuala Livingstone, Cochrane's Editorial and Methods Department (methods); Robin Featherstone, Cochrane's Editorial and Methods Department, (search); Tess Moore, Cochrane's Editorial and Methods Department (methods); Kerry Dwan, Cochrane's Editorial and Methods Department (methods); Nida Qadir, Division of Pulmonary & Critical Care Medicine, David Geffen School of Medicine at UCLA (clinical/content); Jen-Ting Chen, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA (clinical/content); Joseph M. Vinetz, Section of Infectious Diseases, Department of Internal Medicine, Yale School of Medicine (clinical/content) and Ahlam Jamal Alhemedi (consumer).

We thank Dr. Sven Laudi and Dr. Volker Thieme at the Department of Anesthesia and Intensive Care at the Leipzig University Medical Services for their biostatistical advice.

The research was part of a project supported by the German Federal Ministry of Education and Research (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'CEOSys'). The contents of this document reflect only the authors' views and the German Ministry is not responsible for any use that may be made of the information it contains.

REFERENCES

References to studies included in this review

Angus 2020 *{published data only}*

Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, Van Bentum-Puijk W, et al. The randomised embedded multifactorial adaptive platform for community-acquired pneumonia (REMAP-CAP) study: rationale and design. *Annals of the American Thoracic Society* 2020;**17**(7):879-91. [DOI: 10.1513/AnnalsATS.202003-192SD]

* Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomised clinical trial. *JAMA* 2020;**324**(13):1317-29. [DOI: 10.1001/jama.2020.17022] [NCT02735707]

Corral-Gudino 2021 *{published data only}*

* Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, et al. Methylprednisolone in adults hospitalised with COVID-19 pneumonia: an open-label randomised trial (GLUCOCOVID). *Wiener Klinische Wochenschrift* 2021;**133**(7-8):303-11. [DOI: 10.1007/s00508-020-01805-8] [EUCTR2020-001934-37-ES]

Corral L, Bahamonde A, Arnaiz delas Revillas F, Gomez-Barquero J, Abadia-Otero J, Garcia-Ibarbia C, et al. GLUCOCOVID: a controlled trial of methylprednisolone in adults hospitalised with COVID-19 pneumonia. medRxiv [Preprint]. [DOI: 10.1101/2020.06.17.20133579] [EUCTR2020-001934-37-ES]

Dequin 2020 *{published data only}*

Dequin PF, Gouge AL, Tavernier E, Giraudeau B, Zohar S. Embedding a COVID-19 group sequential clinical trial within an ongoing trial: lessons from an unusual experience. Statistics in Biopharmaceutical Research 2020:1-5. [EMBASE: https://www.embase.com/search/results?subaction=viewrecord&id=L2005906375&from=export]

* Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomised clinical trial. *JAMA* 2020;**324**(13):1298-306. [DOI: 10.1001/jama.2020.16761] [NCT02517489]

Edalatifard 2020 *{published data only}*

Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *European Respiratory Journal* 2020;**56**(6):1-13. [DOI: 10.1183/13993003.02808-2020] [IRCT20200404046947N1]

Farahani 2021 *{published data only}*

Farahani RH, Mosaed R, Nezami-Asl A, Chamanara M, Soleiman-Meigooni S, Kalantar S, et al. Evaluation of the efficacy of methylprednisolone pulse therapy in treatment of COVID-19 adult patients with severe respiratory failure: randomised, clinical trial. *Research Square* 2021;**Version 1**:1-19. [DOI: 10.21203/rs.3.rs-66909/v1] [IRCT20200406046963N1]

Horby 2021 *{published data only}*

Horby P, Lim WS, Emberson J, Mafham M, Bell J, Linsell L, et al. Effect of dexamethasone in hospitalised patients with COVID-19: preliminary report. medRxiv [Preprint] 2020. [DOI: https://doi.org/10.1101/2020.06.22.20137273]

* Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalised patients with COVID-19. *New England Journal of Medicine* 2021;**384**(8):693-704. [DOI: 10.1056/NEJMoa2021436] [NCT04381936]

Oxford University. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. University of Oxford 2020.

Jamaati 2021 *{published data only}*

Jamaati H, Hashemian SM, Farzanegan B, Malekmohammad M, Tabarsi P, Marjani M, et al. No clinical benefit of high dose corticosteroid administration in patients with COVID-19: a preliminary report of a randomised clinical trial. *European Journal of Pharmacology* 2021;**897**:173947. [DOI: 10.1016/j.ejphar.2021.173947] [IRCT20151227025726N17]

Jeronimo 2020 *{published data only}*

Jeronimo CM, Farias ME, Val FF, Sampaio VS, Alexandre MA, Melo GC, et al. Methylprednisolone as adjunctive therapy for patients hospitalised with COVID-19 (metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. *Clinical Infectious Diseases* 2020;**72**(9):e373–e81. [DOI: 10.1093/cid/ciaa1177] [NCT04343729]

Ranjbar 2021 *{published data only}*

Ranjbar K, Shahriarirad R, Erfani A, Khodamoradi Z, Saadi MHG, et al. Methylprednisolone or dexamethasone, which one is the superior corticosteroid in the treatment of hospitalised COVID-19 Patients: a triple-blinded randomised controlled trial. Research Square (Preprint). [DOI: https://doi.org/10.21203/rs.3.rs-148529/v1] [IRCT20200204046369N1]

Tang 2021 *{published data only}*

Tang X, Feng YM, Ni JX, Zhang JY, Liu LM, Hu K, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomised control trial. *Respiration* 2021;**100**(2):116-26. [DOI: 10.1159/000512063] [NCT04273321]

Tomazini 2020 *{published data only}*

Tomazini BM, Maia IS, Bueno FR, Silva Mvao Baldassare FP, Costa EL, Moura RA, et al. COVID-19-associated ARDS treated with DEXamethasone (CoDEX): study design and rationale for a randomised trial. medRxiv [Preprint] 2020. [DOI: https://doi.org/10.1101/2020.06.24.20139303]

Tomazini BM, Maia IS, Bueno FR, Silva Mvao Baldassare FP, Costa EL, Moura RA, et al. COVID-19-associated ARDS treated with dexamethasone (CoDEX): study design and rationale for a randomised trial. *Revista Brasileira de Terapia Intensiva* 2020;**32**(3):354-62. [DOI: 10.5935/0103-507X.20200063]

* Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomised clinical trial. *JAMA* 2020;**324**(13):1307-16. [DOI: 10.1001/jama.2020.17021] [NCT04327401]

References to studies excluded from this review

EUCTR2020-001445-39-ES *{published data only}*

EUCTR2020-001445-39-ES. Clinical trial to evaluate methylprednisolone pulses and tacrolimus in hospitalized patients with severe pneumonia secondary to COVID-19 (tacrovid). www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001445-39 (first received 31 March 2020).

EUCTR2020-001616-18-ES *{published data only}*

* TACTIC-COVID. www.clinicaltrialsregister.eu/ctr-search/search?query=2020-001616-18.

Treatment with inhaled corticoids in patients with COVID-19 and pneumonia. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2020-001616-18-ES.

EUCTR2020-001889-10 *{published data only}*

EUCTR2020-001889-10. Use of inhaled corticosteroids as treatment of early COVID-19 infection to prevent clinical deterioration and hospitalisation. www.clinicaltrialsregister.eu/ctr-search/trial/2020-001889-10/GB (first received 15 May 2020).

IRCT20120225009124N4 *{published data only}*

IRCT20120225009124N4. Letter to the editor: efficacy of different methods of combination regimen administrations including dexamethasone, intravenous immunoglobulin, and interferon-beta to treat critically ill COVID-19 patients: a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020;**21**(1):549. [DOI: 10.1186/s13063-020-04499-5]

IRCT20190312043030N2 *{published data only}*

IRCT20190312043030N2. The effect of selenium, vitamin C and methylprednisolone combination on mortality and morbidity of COVID-19 patients. en.irct.ir/trial/49508 (first received 19 August 2020).

IRCT20200522047542N1 *{published data only}*

IRCT20200522047542N1. Effect of corton on olfactory dysfunction in COVID-19 patients. en.irct.ir/trial/48379 (first received 4 August 2020).

ISRCTN86534580 *{published data only}*

ISRCTN86534580. PRINCIPLE: a trial evaluating treatments for suspected COVID-19 in people aged 50 years and above with pre-existing conditions and those aged 65 years and above. www.isrctn.com/ISRCTN86534580 (first received 20 March 2020).

NCT04341038 *{published data only}*

* NCT04341038. Clinical trial to evaluate methylprednisolone pulses and tacrolimus in patients with COVID-19 lung injury. clinicaltrials.gov/show/NCT04341038 (first received 10 April 2020).

NCT04341038. Pragmatic, open-label, single-center, randomized, phase II clinical trial to evaluate the efficacy and safety of methylprednisolone pulses and tacrolimus in patients with severe pneumonia secondary to COVID-19: the TACROVID trial protocol. *medRxiv [Preprint]* 2021;**21**(100716):1-8. [DOI: 10.1016/j.conctc.2021.100716]

NCT04355637 *{published data only}*

NCT04355637. Inhaled corticosteroid treatment of COVID-19 patients with pneumonia. clinicaltrials.gov/show/NCT04355637 (first received 21 April 2020).

NCT04359511 *{published data only}*

NCT04359511. Efficacy and safety of corticosteroids in oxygen-dependent patients with COVID-19 pneumonia. clinicaltrials.gov/show/NCT04359511 (first received 24 April 2020).

NCT04361474 *{published data only}*

Daval M, Corre A, Palpacuer C, Houssette J, Poillon G, Eliezer M, et al. Efficacy of local budesonide therapy in the management of persistent hyposmia in COVID-19 patients without signs of severity: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;**21**(666):1-3. [DOI: https://doi.org/10.1186/s13063-020-04585-8]

* NCT04361474. Trial evaluating the efficacy of local budesonide therapy in the management of hyposmia in COVID-19 patients without signs of severity. clinicaltrials.gov/show/NCT04361474 (first received 24 April 2020).

NCT04381364 *{published data only}*

NCT04381364. Inhalation of ciclesonide for patients with COVID-19: a randomised open treatment study (HALT COVID-19). clinicaltrials.gov/show/NCT04381364 (first received 8 May 2020).

NCT04411667 *{published data only}*

Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, et al. Intravenous immunoglobulin plus methylprednisolone mitigate respiratory morbidity in coronavirus disease 2019. *Critical Care Explorations* 2020;**2**(11):e0280. [DOI: 10.1097/CCE.0000000000000280]

NCT04416399 *{published data only}*

Ramakrishnan S, Nicolau DV Jr, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 illness: a randomised controlled trial. medRxiv [Preprint]. [DOI: https://doi.org/10.1101/2021.02.04.21251134]

NCT04468646 *{published data only}*

Riffat M, Fridoon A, Ahad Q, Muhammad AR, Syed AG, Muhammad AT, et al. Aprepitant as a combinant with dexamethasone reduces the inflammation via neurokinin 1 receptor antagonism in severe to critical COVID-19 patients and potentiates respiratory recovery: a novel therapeutic approach. medRxiv [Preprint]. [DOI: https://doi.org/10.1101/2020.08.01.20166678]

NCT04484493 *{published data only}*

Abdelalim AA, Mohamady AA, Elsayed RA, Elawady MA, Ghallab AF. Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: a randomised controlled trial. *American Journal of Otolaryngology* 2021;**42**(2):1-6. [PMID: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7836546/pdf/main.pdf]

NCT04534478 *{published data only}*

NCT04534478. Oral prednisone regimens to optimise the therapeutic strategy in patients with organising pneumonia post-COVID-19. clinicaltrials.gov/show/NCT04534478 (first received 1 September 2020).

NCT04551781 *{unpublished data only}*

NCT04551781. Short term low dose corticosteroids for management of post COVID19 pulmonary fibrosis. clinicaltrials.gov/show/NCT04551781 (first received 16 September 2020).

NCT04561180 *{published data only}*

NCT04561180. Study to evaluate the efficacy and safety of EG-HPCP-03a compared to DEX in patients with COVID-19 pneumonia. clinicaltrials.gov/show/NCT04561180 (first received 23 September 2020).

NCT04569825 *{published data only}*

NCT04569825. Effect of nasal steroid in the treatment of anosmia due to COVID-19 disease. clinicaltrials.gov/ct2/show/NCT04569825 (first received 30 September 2020).

NCT04640168 *{published data only}*

NCT04640168. Adaptive COVID-19 treatment trial 4 (ACTT-4). clinicaltrials.gov/show/NCT04640168 (first received 23 November 2020).

NCT04657484 *{published data only}*

NCT04657484. Comparison of two corticosteroid regimens for post-COVID diffuse lung disease. clinicaltrials.gov/show/NCT04657484 (first received 8 December 2020).

NCT04826822 *{published data only}*

NCT04826822. Spironolactone and dexamethasone in patients hospitalised with COVID-19 (SPIDEX-II). clinicaltrials.gov/show/NCT04826822 (first received 1 April 2021).

References to studies awaiting assessment

EUCTR2020-001307-16-ES *{published data only}*

EUCTR2020-001307-16-ES. Efficacy and safety of corticoids in patients with adult respiratory distress syndrome (ARDS) secondary to coronavirus infection. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001307-16 (first received 1 April 2020).

EUCTR2020-001333-13-FR *{published data only}*

EUCTR2020-001333-13-FR. Dexamethasone associated with hydroxychloroquine vs. hydroxychloroquine alone for the early treatment of severe ARDS caused by COVID-19: a randomised controlled trial. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001333-13 (first received 9 April 2020).

EUCTR2020-001553-48-FR *{published data only}*

EUCTR2020-001553-48-FR. Corticoids in COVID-19 viral pneumonia in infection with SARS-CoV-2 (translation by the review authors) [Corticoides au cours de la pneumonie virale COVID-19 liee a linfection par le SARS-CoV-2]. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001553-48 (first received 13 April 2020).

IRCT20081027001411N3 *{published data only}*

IRCT20081027001411N3. Effect of prednisolone on treatment of COVID-19. irct.ir/trial/46975 (first received 6 January 2020).

IRCT20100228003449N31 *{published data only}*

IRCT20100228003449N31. Corticosteroids in COVID-19. irct.ir/trial/51163 (first received 8 October 2020).

IRCT20120215009014N354 *{published data only}*

IRCT20120215009014N354. Evaluating the effect of intravenous hydrocortisone, methylprednisolone, and dexamethasone in treatment of patients with moderate to severe acute respiratory distress syndrome caused by COVID-19. irct.ir/trial/48043 (first received 12 May 2020).

IRCT20160118026097N4 *{published data only}*

IRCT20160118026097N4. The effect of dexamethasone in the treatment of high-risk COVID-19 patients. irct.ir/trial/48310 (first received 13 September 2020).

IRCT20200611047727N3 *{published data only}*

IRCT20200611047727N3. Evaluation of efficacy and safety of low dose corticosteroid with severe pneumonia COVID-19. irct.ir/trial/49116 (first received 3 January 2021).

IRCT20201015049030N1 *{published data only}*

IRCT20201015049030N1. Effect of dexamethasone on treatment of COVID-19. www.irct.ir/trial/51736 (first received 7 November 2020).

ISRCTN33037282 *{published data only}*

ISRCTN33037282. Comparing two medications (dexamethasone and methylprednisolone high dose) for the treatment of pneumonia in patients with COVID-19. www.isrctn.com/ISRCTN33037282 (first received 26 November 2020).

Munch 2021 *{published data only}*

* Munch MW, Meyhoff TS, Helleberg M, Kjær M-BN, Granholm A, Hjortsø CJ, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: the COVID STEROID randomised, placebo-controlled trial. Acta Anaesthesiologica Scandinavica 2021 Jun 17 [Epub ahead of print]. [DOI: 10.1111/aas.13941]

NCT04348305. Hydrocortisone for COVID-19 and severe hypoxia. clinicaltrials.gov/show/NCT04348305 (first received 16 April 2020).

Petersen MW, Meyhoff TS, Helleberg M, Nørregaard Kjær MB, Granholm A, Steensen Hjortsø CJ, et al. Low-dose

hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial-protocol and statistical analysis plan. *Acta Anaesthesiologica Scandinavica* 2020;**64**(9):1365-75. [DOI: 10.1111/aas.13673]

NCT03852537 *{published data only}*

NCT03852537. Steroid dosing by biomarker guided titration in critically ill patients with pneumonia. clinicaltrials.gov/show/NCT03852537 (first received 25 February 2019).

NCT04244591 *{published data only}*

NCT04244591. Glucocorticoid therapy for novel coronavirus critically ill patients with severe acute respiratory failure. www.clinicaltrials.gov/ct2/show/NCT04244591 (first received 28 January 2020).

NCT04325061 *{published data only}*

NCT04325061. Efficacy of dexamethasone treatment for patients with ARDS caused by COVID-19. clinicaltrials.gov/ct2/show/NCT04325061 (first received 27 March 2020).

NCT04746430 *{published data only}*

NCT04746430. COVID-19 primary care platform for early treatment and recovery (COPPER) study. clinicaltrials.gov/show/NCT04746430 (first received 9 February 2021).

Rashad 2021 *{unpublished data only}*

NCT04519385. Tocilizumab versus dexamethasone in severe COVID19 cases. clinicaltrials.gov/show/NCT04519385 (first received 19 August 2020).

* Rashad A, Mousa S, Nafady-Hego H, Nafady A, Elgendy H. Short term survival of critically ill COVID-19 Egyptian patients on assisted ventilation treated by either dexamethasone or tocilizumab. *Scientific Reports* 2021;**11**(8816):1-7.

References to ongoing studies

ChiCTR2000029386 *{published data only}*

Qin YY, Zhou YH, Lu YQ, Sun F, Yang S, Harypursat V, et al. Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: protocol of a randomised controlled trial. Chinese Medical Journal 2020;**133**(9):1080-6. [DOI: 10.1097/CM9.0000000000000791] [ChiCTR2000029386]

ChiCTR2000029656 *{published data only}*

ChiCTR2000029656. A randomised, open-label study to evaluate the efficacy and safety of low-dose corticosteroids in hospitalised patients with novel coronavirus pneumonia (COVID-19). www.chictr.org.cn/showprojen.aspx?proj=49086 (first received 9 February 2020).

ChiCTR2000030481 *{published data only}*

ChiCTR2000030481. The clinical value of corticosteroid therapy timing in the treatment of novel coronavirus pneumonia (COVID-19): a prospective randomised controlled trial. www.chictr.org.cn/showprojen.aspx?proj=50453 (first received 3 March 2020).

CTRI/2020/07/026608 *{published data only}*

CTRI/2020/07/026608. A clinical trial to study the effects of two drugs methylprednisolone and dexamethasone in patients with severe COVID-19. www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=45638 (first received 15 July 2020).

CTRI/2020/10/028731 *{published data only}*

* CTRI/2020/10/028731. Higher vs. lower doses of dexamethasone in patients with COVID-19 and severe hypoxia. ctri.nic.in/Clinicaltrials/showallp.php?mid1=46442&EncHid=&userName=28731 (first received 29 October 2020).

CTRI/2020/10/028731. Higher vs. lower doses of steroids in patients with COVID-19. www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/10/028731 (first received 29 October 2020).

CTRI/2020/12/029894 *{published data only}*

* Comparing the effectiveness of dexamethasone versus methylprednisolone in patients with moderate COVID 19 - a randomised controlled trial. ctri.nic.in/Clinicaltrials/showallp.php?mid1=49273&EncHid=&userName=029894 (first received 18 December 2020).

CTRI/2020/12/029894. A study to compare the effectiveness of two drugs, dexamethasone versus methylprednisolone in the treatment of moderate Covid 19 patients. www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/12/029894.

CTRI/2020/12/030143 *{published data only}*

CTRI/2020/12/030143. Comparison of different steroid regimes in critically ill adult patients of COVID-19. www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/12/030143.

* Evaluation of different steroid regimes in critically ill adult patients of COVID-19 admitted to intensive care units. ctri.nic.in/Clinicaltrials/showallp.php?mid1=50886&EncHid=&userName=30143 (first received 31 December 2020).

EUCTR2020-001413-20-ES *{published data only}*

EUCTR2020-001413-20-ES. Efficacy and safety of siltuximab vs. corticosteroids in hospitalized patients with COVID-19 pneumonia. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001413-20 (first received 7 April 2020).

EUCTR2020-001457-43-FR *{published data only}*

EUCTR2020-001457-43-FR. Dexamethasone and oxygen support strategies in ICU patients with COVID-19 pneumonia. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001457-43 (first received 10 April 2020).

EUCTR2020-001622-64-ES *{published data only}*

* EUCTR2020-001622-64-ES. Outpatient treatment of COVID-19 with early pulmonary corticosteroids as an opportunity to modify the course of the disease. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001622-64 (first received 19 April 2020).

Saiz-Rodríguez M, Peña T, Lázaro L, González A, Martínez A, Cordero JA, et al. Outpatient treatment of COVID-19 with steroids in the phase of mild pneumonia without the need for admission as an opportunity to modify the course of the disease: a structured summary of a randomised controlled trial. *Trials* 2020;**21**(632):1-3. [DOI: 10.1186/s13063-020-04575-w]

EUCTR2020-001707-16-ES *{published data only}*

EUCTR2020-001707-16-ES. Phase III randomised, unicentric open, controlled clinical trial to demonstrate the effectiveness of tocilizumab against systemic corticotherapy in patients entered by COVID-19 with bilateral pneumonia and bad evolution. www.clinicaltrialsregister.eu/ctr-search/trial/2020-001707-16/ES (first received 25 June 2020).

EUCTR2020-001921-30 *{published data only}*

Busani S, Tosi M, Mighali P, Vandelli P, D'Amico R, Marietta M, et al. Multi-centre, three arm, randomised controlled trial on the use of methylprednisolone and unfractionated heparin in critically ill ventilated patients with pneumonia from SARS-CoV-2 infection: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;**21**(1):724. [DOI: 10.1186/s13063-020-04645-z]

* EUCTR2020-001921-30. Steroids and unfractionated heparin in critically-ill patients with pneumonia from COVID-19 infection. A multicenter, interventional, randomised, three arms study design. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001921-30 (first received 26 June 2020).

EUCTR2020-002186-34-ES *{published data only}*

EUCTR2020-002186-34-ES. Efficacy of the early use of corticotherapy in CoV-2 infection to prevent the progression of acute respiratory distress syndrome (ARDS). www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-002186-34 (first received 22 July 2020).

EUCTR2020-003363-25-DK *{published data only}*

EUCTR2020-003363-25-DK. Higher vs. lower doses of dexamethasone in patients with COVID-19 and severe oxygen deficiency: the COVID STEROID 2 trial. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-003363-25 (first received 18 August 2020).

EUCTR2020-004323-16 *{published data only}*

EUCTR2020-004323-16. Evaluation of the efficacy of high doses of methylprednisolone in SARS-CoV2 pneumonia patients. www.clinicaltrialsregister.eu/ctr-search/trial/2020-004323-16/IT (first received 23 November 2020).

NCT04329650 *{published data only}*

NCT04329650. Efficacy and safety of siltuximab vs. corticosteroids in hospitalised patients with COVID19 pneumonia. clinicaltrials.gov/show/NCT04329650 (first received 1 April 2020).

NCT04344730 *{published data only}*

NCT04344730. Dexamethasone and oxygen support strategies in ICU patients with COVID-19 pneumonia. clinicaltrials.gov/show/NCT04344730 (first received 14 April 2020).

NCT04345445 *{published data only}*

NCT04345445. Study to evaluate the efficacy and safety of tocilizumab versus corticosteroids in hospitalised COVID-19 patients with high risk of progression. clinicaltrials.gov/show/NCT04345445 (first received 14 April 2020).

NCT04347980 *{published data only}*

NCT04347980. Dexamethasone treatment for severe acute respiratory distress syndrome. clinicaltrials.gov/show/NCT04347980 (first received 15 April 2020).

NCT04377503 *{published data only}*

NCT04377503. Tocilizumab versus methylprednisolone in the cytokine release syndrome of patients with COVID-19. clinicaltrials.gov/show/NCT04377503 (first received 6 May 2020).

NCT04395105 *{published data only}*

Maskin LP, Olarte GL, Palizas F Jr, Velo AE, Lurbet MF, Bonelli I, et al. High dose dexamethasone treatment for acute respiratory distress syndrome secondary to COVID-19: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;**21**(1):743. [DOI: 10.1186/s13063-020-04646-y]

* NCT04395105. Dexamethasone for COVID-19 related ARDS: a multicenter, randomised clinical trial. clinicaltrials.gov/show/NCT04395105 (first received 20 May 2020).

NCT04438980 *{published data only}*

Les Bujanda I, Loureiro-Amigo J, Capdevila Bastons F, Elejalde Guerra I, Anniccherico Sánchez J, Murgadella-Sancho A, et al. Treatment of COVID-19 pneumonia with glucocorticoids (CORTIVID): a structured summary of a study protocol for a randomised controlled trial. *Trials* 2021;**22**(1):43. [DOI: 10.1186/s13063-020-04999-4]

* NCT04438980. Glucocorticoids in COVID-19 (CORTIVID). clinicaltrials.gov/show/NCT04438980 (first received 19 June 2020).

NCT04451174 *{published data only}*

* NCT04451174. Early use of corticosteroids in hospitalised patients with moderate COVID19 pneumonia. clinicaltrials.gov/show/NCT04451174 (first received 30 June 2020).

Salinas M, Andino P, Palma L, Valencia J, Figueroa E, Ortega J. Early use of corticosteroids in non-critical patients with COVID-19 pneumonia (PREDCOVID): a structured summary of a study protocol for a randomised controlled trial. *Trials* 2021;**22**(1):92. [DOI: 10.1186/s13063-021-05046-6.]

NCT04452565 *{published data only}*

NCT04452565. NA-831, atazanavir and dexamethasone in the treatment of SARSCov-2 infection (NATADEX). clinicaltrials.gov/show/NCT04452565 (first received 30 June 2020).

NCT04485429 *{published data only}*

NCT04485429. Efficacy assessment of methylprednisolone and heparin in patients with COVID-19 pneumonia. clinicaltrials.gov/show/NCT04485429 (first received 24 July 2020).

NCT04499313 *{published data only}*

NCT04499313. Dexamethasone versus methylprednisolone for the treatment of patients with ARDS caused by COVID-19. clinicaltrials.gov/show/NCT04499313 (first received 5 August 2020).

NCT04509973 *{published data only}*

Munch MW, Granholm A, Myatra SN, Vijayaraghavan BK, Cronhjort M, Wahlin RR, et al. Higher vs. lower doses of dexamethasone in patients with COVID-19 and severe hypoxia (COVID STEROID 2) trial: protocol and statistical analysis plan. *Acta Anaesthesiologica Scandinavica* 2021;**00**:1-12. [DOI: 10.1111/aas.13795]

* NCT04509973. Higher vs. lower doses of dexamethasone for COVID-19 and severe hypoxia. clinicaltrials.gov/show/NCT04509973 (first received 12 August 2020).

NCT04513184 *{published data only}*

NCT04513184. Randomised clinical trial of nasal dexamethasone as an adjuvant in patients with COVID-19. clinicaltrials.gov/show/NCT04513184 (first received 14 August 2020).

NCT04528329 *{published data only}*

NCT04528329. Anosmia and / or ageusia and early corticosteroid use. clinicaltrials.gov/show/NCT04528329 (first received 27 August 2020).

NCT04528888 *{published data only}*

NCT04528888. Steroids and unfractionated heparin in critically ill patients with pneumonia from COVID-19 infection. clinicaltrials.gov/show/NCT04528888 (first received 27 August 2020). [EUDRA-CT: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001921-30/IT] [NCT: https://clinicaltrials.gov/ct2/show/study/NCT04528888]

NCT04530409 *{published data only}*

NCT04530409. Timing of corticosteroids in COVID-19. clinicaltrials.gov/show/NCT04530409 (first received 28 August 2020).

NCT04545242 *{published data only}*

NCT04545242. Efficacy of dexamethasone in patients with acute hypoxemic respiratory failure caused by infections. clinicaltrials.gov/show/NCT04545242 (first received 10 September 2020).

NCT04636671 *{published data only}*

NCT04636671. Methylprednisolone vs. dexamethasone in COVID-19 pneumonia (MEDEAS RCT). clinicaltrials.gov/show/NCT04636671 (first received 19 November 2020).

NCT04663555 *{published data only}*

NCT04663555. Effect of two different doses of dexamethasone in patients with ARDS and COVID-19. clinicaltrials.gov/show/NCT04663555 (first received 11 December 2020).

NCT04673162 *{published data only}*

NCT04673162. Evaluation of the efficacy of high doses of methylprednisolone in SARS-CoV2 (COVID-19) pneumonia patients. clinicaltrials.gov/show/NCT04673162 (first received 17 December 2020).

NCT04707534 *{published data only}*

NCT04707534. Dexamethasone for COVID-19. clinicaltrials.gov/show/NCT04707534 (first received 13 January 2021).

NCT04726098 *{published data only}*

NCT04726098. Low or high dose of dexamethasone in patients with respiratory failure by COVID-19. clinicaltrials.gov/ct2/show/record/NCT04726098 (first received 27 January 2021).

NCT04765371 *{published data only}*

NCT04765371. Comparison between prednisolone and dexamethasone on mortality in patients on oxygen therapy, with COVID-19. clinicaltrials.gov/ct2/show/NCT04765371 (first received 21 February 2021).

NCT04780581 *{published data only}*

NCT04780581. Glucocorticoid therapy in coronavirus disease COVID-19 patients. clinicaltrials.gov/show/NCT04780581 (first received 3 March 2021).

NCT04795583 *{published data only}*

NCT04795583. Corticosteroids for COVID-19. clinicaltrials.gov/show/NCT04795583 (first received 12 March 2021).

NCT04834375 *{published data only}*

NCT04834375. Randomised open investigation determining steroid dose. clinicaltrials.gov/show/NCT04834375 (first received 8 April 2021).

NCT04836780 *{published data only}*

NCT04836780. Dexamethasone early administration in hospitalised patients with COVID-19 pneumonia. clinicaltrials.gov/show/NCT04836780 (first received 8 April 2021).

Additional references

Barnes 2006

Barnes PJ. How corticosteroids control inflammation: quintiles prize lecture. *British Journal of Pharmacology* 2005;**148**(3):245-54. [DOI: 10.1038/sj.bjp.0706736]

Bourdeau 2003

Bourdeau I, Stratakis CA. Glucocorticoids, Pharmacology of. In: Henry H, Norman A, editors(s). Encyclopedia of Hormones. Vol. -. Cambridge, MA: Academic Press, 2003:142-50. [DOI: https://doi.org/10.1016/B0-12-341103-3/00122-4]

Brock 2011

Brock GN, Barnes C, Ramirez JA, Myers J. How to handle mortality when investigating length of hospital stay and time to clinical stability. *BMC Medical Research Methodology* 2011;**11**:144. [DOI: https://doi.org/10.1186/1471-2288-11-144]

Buitrago-Garcia 2020

Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci Aziz M, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLoS Medicine* 2020;**17**(9):e1003346.

Chaudhuri 2021

Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. *Intensive Care Medicine* 2021;**47**:521–37. [DOI: https://doi.org/10.1007/s00134-021-06394-2]

Columbia Public Health 2021

Competing Risk Analysis. Columbia University Mailman School of Public Health Website. Available from www.publichealth.columbia.edu/research/population-health-methods/competing-risk-analysis (accessed 13 July 2021). [ACCESSED JULY 13 2021: https://www.publichealth.columbia.edu/research/population-health-methods/competing-risk-analysis]

COMET 2020

Core outcome set developers' response to COVID-19. www.comet-initiative.org/Studies/Details/1538 (accessed 2 November 2020).

Deeks 2021

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

EndNote X9 [Computer program]

EndNote X9. Clarivate, 2020.

GRADE pro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed prior to July 2021. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2019

Higgins JP, Savovic J, Page MJ, Sterne JA. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2 (accessed 7 July 2021).

Higgins 2021a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version version 6.2 (updated February 2021). Cochrane, 2021. Available from: training.cochrane.org/handbook 2020.

Higgins 2021b

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Higgins 2021c

Higgins JP, Li T, Deeks JJ, editor(s). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Huang 2020

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**(10223):497-506.

Johns Hopkins University 2021

Johns Hopkins University. Mortality analyses. coronavirus.jhu.edu/data/mortality (accessed 11 March 2021).

Kreuzberger 2021

Kreuzberger N, Hirsch C, Chai KL, Piechotta V, Valk SJ, Estcourt LJ, et al. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013825. [DOI: 10.1002/14651858.CD013825]

Lauer 2020

Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Annals of Internal Medicine* 2020;**172**(9):577–82.

Li 2021

Li T, Higgins JP, Deeks JJ (editors). Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 6.1 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Liang 2020

Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncology* 2020;**21**(3):335-7.

Living Evidence Network 2019

Living Evidence Network. Guidance for the production and publication of Cochrane living systematic reviews: Cochrane Reviews in living mode (Version December 2019). Available

from community.cochrane.org/review-production/production-resources/living-systematic-reviews (accessed 22 March 2021).

Marshall 2020

Marshall JC, Murthy S, Diaz J, Adhikari NK, Angus DC, Arabi YM, et al. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infectious Diseases* 2020;**20**(8):e192-7.

Microsoft 2018 [Computer program]

Microsoft Excel. Microsoft Corporation. Microsoft Corporation, 2018. office.microsoft.com/excel.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12.

Park 2020

Park JJ, Harari O, Dron L, Lester RT, Thorlund K, Mills EJ. An overview of platform trials with a checklist for clinical readers. *Journal of Clinical Epidemiology* 2020;**125**:1-8. [DOI: 10.1016/j.jclinepi.2020.04.025]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Pasin 2021

Pasin L, Navalesi P, Zangrillo A, Kuzovlev A, Likhvantsev V, Hajjar LA, et al. Corticosteroids for patients with coronavirus disease 2019 (COVID-19) with different disease severity: a meta-analysis of randomized clinical trials. *Journal of Cardiothoracic and Vascular Anesthesia* 2021;**35**(2):578-84. [DOI: https://doi.org/10.1053/j.jvca.2020.11.057]

Piechotta 2021

Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 2021, Issue 5. Art. No: CD013600. [DOI: 10.1002/14651858.CD013600.pub4]

Ranganathan 2015

Ranganathan P, Aggarwal R, Pramesh CS. Common pitfalls in statistical analysis: odds versus risk. *Perspectives in Clinical Research* 2015;**6**(4):222–4. [PMID: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640017/]

RevMan Web 2019 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). The Cochrane Collaboration, 2019. revman.cochrane.org.

Rhen 2005

Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids - new mechanisms for old drugs. *New England Journal of Medicine* 2005 ;**353**(16):1711-23. [DOI: 10.1056/NEJMra050541]

Rochwerg 2018

Rochwerg B, Oczkowski SJ, Siemieniuk RA, Agoritsas T, Belley-Cote E, D'Aragon F, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Critical Care Medicine* 2018;**46**(9):1411-20. [PMID: 29979221]

Santesso 2020

Santesso N, Glenton C, Dahm P, Garner P, Akl A, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *Journal of Clinical Epidemiology* 2020;**119**:126-35.

Schulte-Schrepping 2020

Schulte-Schrepping J, Reusch N, Paclik D, Baßler K, Schlickeiser S, Zhang B, et al. Severe COVID-19 is marked by a dysregulated myeloid cell compartment. *Cell* 2020;**182**(6):1419-40.

Schünemann 2021

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Siemieniuk 2020

Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for COVID-19: living systematic review and network meta-analysis. *BMJ* 2020;**370**:m2980. [BMJ: https://www.bmj.com/content/370/bmj.m2980]

Skoetz 2020

Skoetz N, Goldkuhle M, Van Dalen EC, Akl EA, Trivella M, Mustafa RA, et al. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and evidence profiles. *Journal of Clinical Epidemiology* 2020;**118**:124-31.

Sterne 2019

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe N, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Sterne 2020

Sterne JA. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;**324**(13):1330-41.

Stoelting 2006

Stoelting RK, Hiller SC (editors). Chapter Pharmacology. In: Pharmacology & Physiology in Anesthetic Practice. 4 edition. Philadelphia: Lippincott Williams & Wilkins, 2006:462.

Struyf 2020

Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database of*

Systematic Reviews 2020, Issue 7. Art. No: CD013665. [DOI: 10.1002/14651858.CD013665]

Thibeault 2021

Thibeault C, Mühlemann B, Helbig ET, Mittermaier M, Lingscheid T, Tober-Lau P, et al. Clinical and virological characteristics of hospitalised COVID-19 patients in a German tertiary care centre during the first wave of the SARS-CoV-2 pandemic: a prospective observational study. *Infection* 2021;**-**:1-12.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [DOI: 10.1186/1745-6215-8-16]

Tong 2020

Tong A, Elliott JH, Azevedo LC, Baumgart A, Bersten A, Cervantes L, et al. Core outcomes set for trials in people with coronavirus disease 2019. *Critical Care Medicine* 2020;**48**(11):1622–35. [PMID: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7448717/]

Van Paassen 2020

Van Paassen J, Vos JS, Hoekstra EM, Neumann KM, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Critical Care* 2020;**24**(696):1-22.

Villar 2020

Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respiratory Medicine* 2020;**8**(3):267-76.

WHO 2007

World Health Organization. Cumulative number of reported probable cases of SARS. www.who.int/csr/sars/country/2003_07_11/en (accessed 22 March 2021).

WHO 2019

World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). www.who.int/emergencies/mers-cov/en (accessed 22 March 2021).

WHO 2020a

World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report (accessed 22 March 2021).

WHO 2020b

World Health Organization. Estimating mortality from COVID-19 - scientific brief. www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Mortality-2020.1 (accessed 22 March 2021).

WHO 2020c

WHO working group on the clinical characterisation and management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infectious Diseases 2020;**20**(8):e192-7.

WHO 2021a

World Health Organization. WHO coronavirus disease (COVID-19) dashboard. covid19.who.int (accessed 1 March 2021).

WHO 2021b

World Health Organization. Weekly epidemiological update - 23 February 2021. www.who.int/publications/m/item/weekly-epidemiological-update---23-february-2021 (accessed 1 March 2021).

WHO 2021c

World Health Organization. SARS-CoV-2 variants. Available from www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/ (accessed 22 March 2021).

WHO Living Guidance 2021

World Health Organization 2021. COVID-19 Clinical management: living guidance. 6. Who do the recommendations apply to? www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1 2021;(3):14. [WHO WEBSITE: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1]

WHO Living Guideline 2021

WHO. Therapeutics and COVID-19: living guideline. Systemic corticosteroids. www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2;(3):37-50. [WHO WEBSITE: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1]

Williamson 2020

Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430-6. [DOI: 10.1038/s41586-020-2521-4]

World Bank Country Groups 2021

World Bank Country and Lending Groups. datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed 15 April 2021). [WEBSITE: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups]

Wu 2020

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**(13):1239-42. [DOI: 10.1001/jama.2020.2648]

Yehya 2019

Yehya, Harhay, Curely et al. Reappraisal of ventilator-free days in critical care research. *American Journal of Respiratory and Critical Care Medicine* 2019;**200**(7):828-36. [DOI: https://doi.org/10.1164/rccm.201810-2050CP]

References to other published versions of this review

Wagner 2021

Wagner C, Griesel M, Micholajewska A, Fichtner F, Skoetz N. Corticosteroids for the treatment of COVID-19 (part of German Ecosystem CEO-Sys). PROSPERO 1 February 2021 (available from www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=227450). [PROSPERO: CRD42020227450]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Angus 2020

Study characteristics	
Methods	Trial design: multicenter, open-label, platform RCT Type of publication: journal publication Setting: inpatient Recruitment dates: 9 March-17 June 2020 Country: Australia, Canada, France, Ireland, the Netherlands, New Zealand, UK, USA Language: English Number of centres: 121 clinical sites Trial registration number: NCT02735707 Date first posted: 13 April 2016
Participants	Age: mean age of • 60.4 years (SD 11.6) in the fixed-dose intervention group; • 59.5 years (SD 12.7) in the shock-dependent intervention group; • 59.9 years (SD 14.6) in the control group Gender: • 98 male (71.5%) and 39 female (28.5%) in the fixed-dose intervention group; • 103 male (70.6%) and 43 female (29.5%) in the shock-dependent intervention group; • 72 (71.3%) male and 29 female (28.7%) in the control group Proportion of confirmed infections • Positive: 81.3% fixed-dose intervention arm 69.6% shock-dependent intervention, 79% in the control arm • Negative: not reported • Unclear: not reported Ethnicity • White: 71.2% in fixed-dose intervention group; 76.2% in the shock-dependent intervention group; 57% in the control group • Asian: 16.2% in fixed-dose intervention group; 10.5% in the shock-dependent intervention group; 27.9% in the control group • Black: 3.6% in fixed-dose intervention group; 6.7% in the shock-dependent intervention group; 5.1% in the control group • Mixed: 3.6% in fixed-dose intervention group; 0% in the shock-dependent intervention group; 2.5% in the control group

Angus 2020 *(Continued)*

- Other: 5.4% in fixed-dose intervention group; 6.7% in the shock-dependent intervention group; 7.6% in the control group

Number of participants (recruited/allocated/evaluated)

- Recruited: 614
- Allocated: 143 fixed-dose intervention group; 152 shock-dependent intervention group; 108 control group
- Evaluated: 137 fixed-dose intervention group; 141 shock-dependent group; 101 control group

Severity of condition according to study definition

- Fixed-dose intervention group
  - None/supplemental oxygen only: 0%
  - HFNC: 12.4%
  - IV only: 24.1%
  - IMV: 63.5%
  - ECMO: 0.7%
  - Vasopressor support: 40.9%
- Shock-dependent intervention group
  - None/supplemental oxygen only: 0.7%
  - HFNC: 15.8%
  - NIV only: 33.6%
  - IMV: 50%
  - ECMO: 0%
  - Vasopressor support: 32.2%
- Control group
  - None/supplemental oxygen only: 0%
  - HFNC: 15.8%
  - NIV only: 31.7%
  - IMV: 52.5%
  - ECMO: 2.0%
  - Vasopressor support: 29.7%

Severity of condition according to WHO score: severe ≥ 6

Co-morbidities: diabetes, respiratory disease, kidney disease, severe cardiovascular disease, immuno-suppressive disease

Inclusion criteria

- Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (COVID-19) infection
- Severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an ICU

Exclusion criteria

- Death is deemed to be imminent and inevitable during the next 24 h AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
- Patient is expected to be discharged from hospital today or tomorrow
- > 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection
- Previous participation in this REMAP within the last 90 days
- Known hypersensitivity to hydrocortisone
- Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP/COVID-19 (or direct complications of CAP/COVID-19), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jiroveci* pneumonia

Angus 2020 *(Continued)*

- > 36 h have elapsed since ICU admission (noting that this may be operationalised as > 24 h has elapsed since commencement of sustained organ failure support)
- Patient has been randomised in a trial evaluating corticosteroids, where the protocol of that trial requires ongoing administration of study drug
- The treating clinician believes that participation in the domain would not be in the best interests of the patient
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): yes

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses)
	• Type of corticosteroid: hydrocortisone
	• Dose:
	  ○ Fixed-dose: 50 mg every 6 h for 7 days
	  ○ Shock-dependent: 50 mg every 6 h for up to 28 days if in shock
	• Route of administration: IV
	Treatment details of control group (e.g dose, route of administration, number of doses)
	• No hydrocortisone
	• Concomitant therapy (e.g description of standard care): not reported
	Duration of follow-up: follow-up ended 12 August 2020
	Treatment cross-overs: no
	Compliance with assigned treatment: yes

Outcomes	Primary study outcome: respiratory and cardiovascular organ support-free days up to day 21, with subcomponents in-hospital deaths and organ support-free days among survivors
	Review outcomes: inpatient setting
	• All-cause mortality at day 21, or longest observation period: reported
	• Improvement of clinical status during the observation period
	  ○ Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
	  ○ Ventilator-free days and alive: not reported
	• Worsening of clinical status during observation period:
	  ○ New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
	• Need for dialysis (at up to 28 days): not reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
	• SAEs: reported
	• AEs (any grade): not reported
	• Hospital-acquired infections: not reported
	Additional study outcomes: time to death, cardiovascular organ support–free days, length of ICU stay, WHO scale at day 14

Identification	
Notes	Date of publication: 2 September 2020 Sponsor/funding: Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium by the European Union, FP7-HEALTH-2013-INNOVATION-1 (grant 602525), the Australian National Health and Medical Research Council (grant APP1101719), the New Zealand Health Research

Angus 2020 *(Continued)*

	Council (grant 16/ 631), the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program (grant 158584), the UK National Institute for Health Research (NIHR) and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (grant CTN 2014-012), the UPMC Learning While Doing Program, the Breast Cancer Research Foundation, the French Ministry of Health (grant PHRC-20-0147), and the Minderoo Foundation Risk of bias table presents two entries for analysis 1.1 All-cause mortality and anaysis 1.5 Serious adverse events: one entry for fixed-dose arm and one for shock-dependent arm

Corral-Gudino 2021

Study characteristics	
Methods	Trial design: multicentric, open-label, RCT Type of publication: journal publication Setting: inpatient Recruitment dates: not reported Country: Spain Language: English Number of centres: 5 hospitals Trial registration number: EUCTR 2020-001934-37 Date of trial registration: 8 May 2020
Participants	Age: mean age of: • 73 years (SD +/- 11) in the intervention group; • 66 years (SD +/- 12) in the control group Gender: • 23 male (66%) in the intervention group • 16 male (55%) in the control group Proportion of confirmed infections: PCR positivity inclusion criterion Ethnicity: not reported Number of participants (recruited/allocated/evaluated): • recruited: 86 • allocated: 35 intervention group and 29 control group • evaluated: 35 intervention group and 29 control group Severity of condition according to study definition • PaO2/FiO2 or PaFi < 300 • SaO2/FiO2 or SaFi < 400 or • At least 2 criteria of the BRESCIA-COVID Respiratory Severity Scale (BCRSS) Severity of condition according to WHO score: moderate to severe 5-6 Co-morbidities: hypertension, cardiac disease, respiratory disease, diabetes

Corral-Gudino 2021 *(Continued)*

	Inclusion criteria
	• Confirmed SARS CoV 2 infection
	• Symptom duration of at least 7 days
	• Radiological evidence of lung disease on chest X-ray or CT scan
	• Moderate to severe disease with abnormal gas exchange:
	  ◦ PaO2/FiO2 or PaFi < 300
	  ◦ SaO2/FiO2 or SaFi < 400 or
	  ◦ At least 2 criteria of the BRESCIA-COVID Respiratory Severity Scale (BCRSS)
	
	Exclusion criteria:
	• Mechanical ventilation
	• Hospitalised in the ICU
	• Treated with corticosteroids or immunosuppressive drugs
	• Chronic kidney disease on dialysis
	• Pregnant
	• Previous treatments: not reported

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses) • Type of corticosteroid: methylprednisolone • Dose: 40 mg for 3 days and then 20 mg for 3 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration, number of doses): standard care • Concomitant therapy (e.g description of standard care): standard care included acetaminophen, oxygen therapy, low molecular weight heparin and antibiotics; azithromycin, hydroxychloroquine and lopinavir plus ritonavir Duration of follow-up: until hospital discharge or day 28 after inclusion Treatment cross-overs: no Compliance with assigned treatment: yes

Outcomes	Primary study outcome: composite endpoint including in-hospital all-cause mortality, escalation to ICU admission or progression of respiratory insufficiency that required noninvasive ventilation
	
	Review outcomes: inpatient setting
	• All-cause mortality at day 21, or longest observation period: reported
	• Improvement of clinical status during observation period:
	  ◦ Liberation from IMV in patients i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with patients alive and ventilated: not reported
	  ◦ Ventilator-free days and alive: not reported
	• Worsening of clinical status during observation period:
	  ◦ New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
	• Need for dialysis (at up to 28 days): not reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
	• SAEs: not reported
	• AEs (any grade): reported
	• Hospital-acquired infections: reported

Corral-Gudino 2021 *(Continued)*

	Additional study outcomes: composite endpoint included in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required noninvasive ventilation
Identification	
Notes	Date of publication: 3 February 2021 Sponsor/funding: IDIVAL Instituto de Investigación Sanitaria Valdecilla

Dequin 2020

Study characteristics	
Methods	Trial design: multicenter, double-blind randomised trial Type of publication: journal publication Setting: inpatient Recruitment dates: 7 March-1 June 2020 Country: France Language: English Number of centres: 9 Trial registration number: NCT02517489 Date first posted: 7 August 2015

Participants	Age:
	
	• median age 63.1 years (IQR 51.5-70.8) in the intervention group
	• median age 66.3 years (IQR 53.5-72.7) in the control group
	
	Gender:
	
	• 54 male (71.1%) and 22 female (28.9%) in the intervention group
	• 50 male (68.5%) and 23 female (31.5%) in the control group
	
	Proportion of PCR-confirmed infections
	
	• Positive: 94.7% intervention arm, 98.8% control arm
	• Negative: not reported
	• Unclear: not reported
	
	Ethnicity: not reported
	
	Number of participants (recruited/allocated/evaluated):
	
	• recruited: 40
	• allocated: 76 intervention group and 73 control group
	• evaluated: 76 in intervention group and 73 in the control group
	
	Severity of condition according to study definition
	
	• Mechanical ventilation (included noninvasive ventilation):
	  ◦ 81.6% in the intervention group
	  ◦ 59% in the control group

Dequin 2020 *(Continued)*

- High-flow oxygen therapy:
  - 13.2% in the intervention group
  - 12.3% in the control group
- Nonrebreathing mask with reservoir bag:
  - 5.3%% in the intervention group
  - 6.8% in the control group

Severity of condition according to WHO score: moderate to severe ≥ 5

Co-morbidities: diabetes, COPD/asthma, immunosuppression

Inclusion criteria

- Admitted to 1 of the 9 participating French ICUs for acute respiratory failure
- At least 18 years of age
- Biologically confirmed (RT-PCR) or suspected (suggestive chest CT scan result in the absence of any other cause of pneumonia) COVID-19
- 1 of 4 severity criteria had to be present:
  - Need for mechanical ventilation with a PEEP of ≥ 5 cm H2O
  - A ratio of PaO2 to FIo2 < 300 on high-flow oxygen therapy with an FIO2 value of at least 50%
  - For participants receiving oxygen through a reservoir mask, a PaO2:FIO2 ratio < 300, estimated using prespecified charts;
  - Or a Pulmonary Severity Index > 130

Exclusion criteria

- Unable to meet inclusion deadlines
- Included in another interventional trial
- Septic shock
- Long-term corticosteroid therapy
- Did not meet severity criteria
- Transferred to another ICU
- Medical team declined enrolment
- Under judicial protection
- Do-not-intubate order
- Moribund
- Declined to participate
- Required hydrocortisone for other medical condition
- Miscellaneous
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): yes

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses): • Type of corticosteroid: hydrocortisone • Dose: 200 mg/day until day 7, then 100 mg/day for 4 days and 50mg/day for 3 days, for a total of 14 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration, number of doses): Placebo Concomitant therapy (e.g description of standard care): not reported Duration of follow-up: last follow-up on 29 June 2020 Treatment cross-overs: no Compliance with assigned treatment: yes

Dequin 2020 *(Continued)*

Outcomes	Primary study outcome: treatment failure on day 21 (death or persistent dependence of mechanical ventilation or high-flow oxygen therapy)
	
	Review outcomes:
	
	Inpatient setting:
	
	• All-cause mortality at day 21, or longest observation period: reported
	• Improvement of clinical status during observation period:
	  ○ Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
	  ○ Ventilator-free days and alive: not reported
	• Worsening of clinical status during observation period:
	  ○ New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
	• Need for dialysis (at up to 28 days): not reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
	• SAEs: reported
	• AEs (any grade): reported
	• Hospital-acquired infections: reported
	
	Additional study outcomes: endotracheal intubation (for patients noninvasively ventilated at inclusion), prone position, ECMO, inhaled nitric oxide

Identification	
Notes	Date of publication: 6 October 2020 Sponsor/funding: University Hospital, Tours

Edalatifard 2020

Study characteristics	
Methods	Trial design: RCT Type of publication: journal publication Setting: inpatient Recruitment dates: 28 March-28 May 2020 (study register entry) Country: Iran Language: English Number of centres: 4 Trial registration number: IRCT20200404046947N1 Date of trial registration: 15 April 2020
Participants	Age • Mean age 55.8 ± 16.35 years in the intervention group

Edalatifard 2020 *(Continued)*

- Mean age 61.7 ± 16.62 years in the control group

Gender:

- 4 male (70.6%) and 10 female (29.4%) in the intervention group
- 15 male (53.6%) and 13 female (46.4%) in the control group

Proportion of confirmed infections: PCR positivity inclusion criterion

Ethnicity: not reported

Number of participants (recruited/allocated/evaluated)

- recruited: 151 recruited
- allocated: 34 in the intervention group and 34 in the control group
- evaluated: 34 in the intervention group and 28 in the control group

Severity of condition according to study definition

- Nasal cannula:
  - 11.8% in the intervention group
  - 32.1% in the control group
- Simple mask:
  - 14.7% in the intervention group
  - 7.1% in the control group
- Reserve mask:
  - 35.3% in the intervention group
  - 21.4% in the control group
- NIV:
  - 38.2% in the intervention group
  - 35.7% in the control group

Severity of condition according to WHO score: moderate to severe 5-6

Co-morbidities: diabetes, hypothyroidism, cancer, respiratory disorder, renal disorder, cardiovascular disorder, hypertension, autoimmune and neurodegenerative diseases

Inclusion criteria

- Aged ≥ 18 years
- Confirmed COVID-19 (RT-PCR) with blood oxygen saturation < 90%, elevated C-reactive protein (CRP > 10), and interleukin (IL)-6 (> 6) at the early pulmonary phase of disease before connecting to the ventilator and intubation
- Agreed to give informed consent

Exclusion criteria

- Patients were intolerant or allergic to any therapeutic agents used in this research
- Pregnant or lactating women
- Patients with blood oxygen saturation < 75%, positive pro-calcitonin (PCT) and troponin test, ARDS, uncontrolled hypertension (HTN), uncontrolled diabetes mellitus (DM), gastrointestinal problems or gastrointestinal bleeding (GIB) history, heart failure (HF), active malignancies and received any immune-suppressor agents
- Previous treatments: not reported

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses): • Type of corticosteroid: methylprednisolone • Dose: 25 0mg/day for 3 days • Route of administration: IV

Edalatifard 2020 *(Continued)*

	Treatment details of control group (e.g dose, route of administration, number of doses): standard care • Concomitant therapy (e.g description of standard care): standard of care included hydroxychloroquine sulphate, lopinavir and naproxen Duration of follow-up: 3 days Treatment cross-overs: no Compliance with assigned treatment: 6 patients in the control group received the intervention drug

Outcomes	Primary study outcome: time to event (discharge or death), time to improvement
	Review outcomes: inpatient setting
	• All-cause mortality at day 21, or longest observation period: not reported
	• Improvement of clinical status during observation period:
	  ○ Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
	  ○ Ventilator-free days and alive: not reported
	• Worsening of clinical status during observation period:
	  ○ New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
	• Need for dialysis (at up to 28 days): not reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
	• SAEs: not reported
	• AEs (any grade): reported
	• Hospital-acquired infections: reported
	Additional study outcomes: blood SO2 level, BORG score, heart rate, temperature, respiratory rate

Identification	
Notes	Date of publication: September 7, 2020 Sponsor/funding: Tehran University of Medical Sciences

Farahani 2021

Study characteristics	
Methods	Trial design: open-label, single-centre RCT Type of publication: preprint Setting: inpatient Recruitment dates: 30 March-18 May 2020 (only estimated dates from registry entry) Country: Iran Language: English Number of centres: 1 Trial registration number: IRCT20200406046963N1

Farahani 2021 *(Continued)*

	Date of trial registration: 22 April 2020
Participants	Age: 18-90 years Gender: no sexes excluded Proportion of confirmed infections: PCR positivity inclusion criterion Ethnicity: no ethnicities excluded Number of participants (recruited/allocated/evaluated): 14 intervention group, 15 control group Severity of condition according to study definition: • moderate to severe COVID-19 admitted to ICU • PaO2/FiO2 < 300 • progression of disease severity and not responding to standard treatment • prediction of intubation for next 24 h Severity of condition according to WHO score: moderate-severe 5-6 Co-morbidities: not reported Inclusion criteria • Confirmed SARS CoV 2 infection • Moderate-severe COVID-19 • Admitted to ICU • PaO2/FiO2, < 300 • Progression of disease severity and not responding to standard treatment • Prediction of intubation for next 24 h Exclusion criteria • Uncontrolled diabetes mellitus • Active GI bleeding • History of corticosteroid hypersensitivity • Severe electrolyte imbalances • Procalcitonin > 0.5 active bacterial • Viral (HIV, hepatitis) and fungal infection Previous treatments: not specified
Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses): 1000 mg methylprednisolone IV for 3 days followed by 1 mg/kg oral prednisolone with dose tapering for 7 days + standard care Treatment details of control group (e.g dose, route of administration, number of doses): standard care Concomitant therapy (e.g. description of standard care): • Kaletra (lopinavir/ritonavir) daily • Hydroxychloroquine 400 mg daily • Azithromycin 500 mg daily Duration of follow-up: not specified Treatment cross-overs: none reported Compliance with assigned treatment: no deviations reported
Outcomes	Primary study outcome: mortality rate, blood O2 saturation and need for further oxygen therapy

Farahani 2021 *(Continued)*

Review outcomes: inpatient setting

- All-cause mortality at day 21, or longest observation period: not reported
- Improvement of clinical status during observation period:
  - Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
  - Ventilator-free days and alive: not reported
- Worsening of clinical status during observation period:
  - New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
- Need for dialysis (at up to 28 days): not reported
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
- Serious adverse events: not reported
- Adverse events (any grade): not reported
- Hospital-acquired infection: not reported

Additional study outcomes

- Glasgow Coma Scale: daily for 10 days mean, although scale is not metric
- Means of SpO2, FiO2, blood pressure, PEEP, CPK, LDH for 10 days

Identification	
Notes	Date of publication: 9 September 2020 Sponsor/funding: Artesh University of Medical Sciences

Horby 2021

Study characteristics	
Methods	Trial design: open-label RCT Type of publication: journal publication Setting: inpatient Recruitment dates: recruitment ended on 8 June 2020 Country: UK Language: English Number of centres: 176 Trial registration number: NCT04381936 Date of trial registration: 11 May 2020
Participants	Age: mean age • 66.9 ± 15.4 years in the intervention group • 65.8 ± 15.8 years in the control group Gender

Horby 2021 *(Continued)*

- 1338 male (64%) and 766 female (36%) in the intervention group
- 2749 male (64%) and 1572 female (36%) in the control group

Proportion of PCR test results

- Positive: 89% intervention arm, 90% control arm
- Negative: 11% intervention arm, 10% control arm
- Unclear: 1% intervention arm, < 1% control arm

Ethnicity: not reported

Number of participants (recruited/allocated/evaluated):

- recruited: 11,303
- allocated: 2104 in the intervention group and 4321 in the control group
- evaluated: 2104 in the intervention group and 4321 in the control group

Severity of condition according to study definition

- No oxygen: 501 (24%) intervention group; 1034 (24%) control group
- Oxygen only: 1279 (61%) intervention group; 2604 (60%) control group
- IMV: 324 (15%) intervention group; 683 (16%) control group

Severity of condition according to WHO score: moderate to severe 4-9

Co-morbidities: diabetes, heart disease, chronic lung disease, tuberculosis, HIV infection, severe liver disease, severe kidney impairment

Inclusion criteria

- Clinically suspected or laboratory confirmed SARS-CoV-2 infection
- Hospitalised patients: no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

Exclusion criteria

- If the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient.
- For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial.

Previous treatments: not reported

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses) • Type of corticosteroid: dexamethasone • Dose: 6 mg once daily for up to 10 days (or until hospital discharge if sooner) • Route of administration: IV or oral Treatment details of control group (e.g dose, route of administration, number of doses) • standard care Concomitant therapy (e.g description of standard care): none Duration of follow-up: until discharge or death, or 28 days after randomisation Treatment cross-overs: no Compliance with assigned treatment: 8% in the control group received intervention drug

Horby 2021 *(Continued)*

Outcomes	Primary study outcome: 28-day mortality
	
	Review outcomes: inpatient setting
	
	• All-cause mortality at day 21, or longest observation period: reported
	• Improvement of clinical status during observation period:
	  ○ Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
	  ○ Ventilator-free days and alive: not reported
	• Worsening of clinical status during observation period:
	  ○ New need for invasive mechanical ventilation i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
	• Need for dialysis (at up to 28 days): not reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
	• Serious adverse events: not reported
	• Adverse events (any grade): not reported
	• Hospital-acquired infections: not reported
	
	Additional study outcomes: composite outcome IMV or death

Identification	
Notes	Date of publication: 17 July 2020 Sponsor/funding: University of Oxford

Jamaati 2021

Study characteristics	
Methods	Trial design: RCT Type of publication: journal publication Setting: inpatient Recruitment dates: March 2020 Country: Iran Language: English Number of centres: 1 Trial registration number: IRCT20151227025726N17 Date of trial registration: 31 May 2020
Participants	Age: median age • Intervention group survivor: 54 years (IQR 37–63) • Intervention group non-survivor: 63 years (IQR 55.5–72.5) • Control group survivor: 61.5 years (IQR 54–62) • Control group non-survivor: 67 years (IQR 48–73)

Jamaati 2021 *(Continued)*

	Gender • 6 male (67%) in the intervention group survivor • 12 male (75%) in the intervention group non-survivor • 7 male (70%) in the control group survivor • 11 male (73%) in the control group non-survivor Proportion of confirmed infections: PCR positivity inclusion criterion Ethnicity: not reported Number of participants (recruited/allocated/evaluated): • recruited: no information • allocated: 25 intervention group and 25 control group • evaluated: 25 intervention group and 25 control group Severity of condition according to study definition: PaO2/FiO2 between 100 and 300 mmHg Severity of condition according to WHO score: most likely 5, no invasive ventilation at randomisation Co-morbidities: diabetes, hypertension, cardiovascular disease Inclusion criteria • Age > 18 years • SARS-CoV-2 infection confirmed by RT-PCR • PaO2/FiO2 between 100 and 300 mmHg • Bilateral lung infiltration • Provision of written informed consent by the patient Exclusion criteria • Patients with chronic kidney diseases • Patients with chronic liver diseases • Patients with hyperglycaemia • Pregnant or breastfeeding women Previous treatments: not reported
Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses) • Type of corticosteroid: dexamethasone • Dose: 20 mg/d from day 1–5 and then at 10 mg/d from day 6–10 • Route of administration: IV Treatment details of control group (e.g dose, route of administration, number of doses) • Standard care Concomitant therapy (e.g description of standard care): oxygen support, fluid support, lopinavir/ritonavir (200/50 mg, 2 tablets twice a day) Duration of follow-up: 28 days Treatment cross-overs: no Compliance with assigned treatment: yes
Outcomes	Primary study outcome: need for IMV, death rate Review outcomes: inpatient setting

Jamaati 2021 *(Continued)*

- All-cause mortality at day 21, or longest observation period: reported
- Improvement of clinical status during observation period:
  - Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
  - Ventilator-free days and alive: not reported
- Worsening of clinical status during observation period:
  - New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
- Need for dialysis (at up to 28 days): not reported
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
- Serious adverse events: not reported
- Adverse events (any grade): not reported
- Hospital-acquired infections: not reported

Additional study outcomes: duration of clinical improvement, radiological changes in the CT scan

Identification	
Notes	Date of publication: 16 February 2021 Sponsor/funding: Shahid Beheshti University of Medical Sciences

Jeronimo 2020

Study characteristics	
Methods	Trial design: double-blind RCT Type of publication: journal publication Setting: inpatient Recruitment dates: not reported Country: Brazil Language: English Number of centres: 1 Trial registration number: NCT04343729 Date of trial registration: 13 April 2020
Participants	Age: mean age • 54 years (SD 15) in the intervention group; • 57 years (SD 15) in the control group Gender • 68 female (35.1%) in the intervention group • 71 female (35.7%) in the control group Proportion of PCR test results

Jeronimo 2020 *(Continued)*

- Positive: 83.4% intervention arm, 79.3% control arm
- Negative: not reported
- Unclear: not reported

Ethnicity: white, black, admixed, Asian, Amerindian

Number of participants (recruited/allocated/evaluated)

- Recruited: 425
- Allocated: 209 intervention group and 207 in the control group
- Evaluated: 195 intervention group and 202 control group

Severity of condition according to study definition

- IMV at baseline: 66 (34%) intervention group and 67 (33.7%) control group
- Non-invasive oxygen therapy at baseline: 98 (50.5%) intervention group and (45.2%) 90 control group

Severity of condition according to WHO score: moderate to severe: 5-9

Co-morbidities: diabetes, hypertension, alcohol use disorder, heart disease, asthma, rheumatic disease, liver disease, previous tuberculosis, COPD

Inclusion criteria

- Clinical and/or radiological suspicion of COVID-19 (history of fever and any respiratory symptom; eg, cough or dyspnoea and/or ground glass opacity or pulmonary consolidation on CT scan)
- Aged ≥ 18 years
- Either had SpO2 ≤ 94% with room air, required supplementary oxygen, or required IMV

Exclusion criteria

- History of hypersensitivity to methylprednisolone
- Living with HIV or AIDS
- Had a history of chronic use of corticosteroids or immunosuppressive agents
- Were pregnant or breastfeeding
- Had decompensated cirrhosis or chronic renal failure

Previous treatments: not reported

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses): • Type of corticosteroid: methylprednisolone • Dose: 0.5 mg/kg twice daily for 5 days • Route of administration: IV • Treatment details of control group (e.g dose, route of administration, number of doses): placebo • Concomitant therapy (e.g description of standard care): all patients meeting ARDS criteria used preemptive IV ceftriaxone (1 g twice a day for 7 days) plus azithromycin (500 mg once a day for 5 days) or clarithromycin (500 mg twice a day for 7 days), starting on day 1 • Duration of follow-up: 28 days • Treatment cross-overs: no • Compliance with assigned treatment: yes
Outcomes	Primary study outcome: 28-day mortality Review outcomes: inpatient setting • All-cause mortality at day 21, or longest observation period: reported

Jeronimo 2020 *(Continued)*

- Improvement of clinical status during observation period:
  - Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
  - Ventilator-free days and alive: not reported
- Worsening of clinical status during observation period:
  - New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): reported
- Need for dialysis (at up to 28 days): reported
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: reported
- Serious adverse events: not reported
- Adverse events (any grade): not reported
- Hospital-acquired infections: not reported

Additional study outcomes:

Identification	
Notes	Date of publication: 12 August 2020 Sponsor/funding: Fundação de Medicina Tropical Dr. Heitor Vieira Dourado

Ranjbar 2021

Study characteristics	
Methods	Trial design: triple-blind RCT Type of publication: preprint Setting: inpatient Recruitment dates: 10 August 2020-15 November 2020 Country: Iran Language: English Number of centres: 1 Trial registration number: IRCT20200204046369N1 Date of trial registration: 8 April 2020
Participants	Age: mean age • 56.2 years (SD ± 17.5) in the intervention group • 61.3 years (SD ± 17.3) in the control group Gender • 27 male (61.4%) and 17 female (38.6%) in the intervention group • 22 male (52.4%) and 20 female (47.6%) in the control group Proportion of confirmed infections: PCR positivity inclusion criterion Ethnicity: not reported

Ranjbar 2021 *(Continued)*

	Number of participants (recruited/allocated/evaluated): • recruited: 86 • allocated: 44 in the intervention group and 42 in the control group • evaluated: 44 in the intervention group and 42 in the control group Severity of condition according to study definition: patients with SpO2 < 92 in room air Severity of condition according to WHO score: moderate 4-5 Co-morbidities: diabetes, cardiovascular disease, hypertension, renal diseases, liver diseases Inclusion criteria • Age > 18 years • Confirmed SARS CoV 2 infection • Hospitalised • SpO2 saturation < 92 in room air Exclusion criteria: Pregnancy • Uncontrolled diabetes mellitus • Uncontrolled hypertension • Previously been treated with steroids • Any contraindication of steroid administration • Immunodeficiency disorders • SpO2 > 92 in room air Previous treatments: not reported
Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses) • Type of corticosteroid: methylprednisolone • Dose: 2 mg/kg daily infused over 60 min, tapered to half dosage every 5 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration, number of doses): 6 mg of dexamethasone IV daily for 10 days Concomitant therapy (e.g description of standard care): no Duration of follow-up: 28 days Treatment cross-overs: no Compliance with assigned treatment: yes

Outcomes	Primary study outcome: all-cause mortality in 28 days, clinical status after 5 and 10 days after enrolment with 9-point WHO scale
	
	Review outcomes: inpatient setting:
	• All-cause mortality at day 21, or longest observation period: reported
	• Improvement of clinical status during observation period:
	  ◦ Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
	  ◦ Ventilator-free days and alive: not reported

Ranjbar 2021 *(Continued)*

- Worsening of clinical status during observation period:
  - New need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
- Need for dialysis (at up to 28 days): not reported
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported
- Serious adverse events: not reported
- Adverse events (any grade): not reported
- Hospital acquired infections: not reported
- Additional study outcomes: intubation, admission to ICU, hospital death during 28 days after enrolment

Identification	
Notes	Date of publication: 1 February 2021 Sponsor/funding: Shiraz University of Medical Sciences Dr. Mohsen Moghadami

Tang 2021

Study characteristics	
Methods	Trial design: prospective, multicenter, single-blind RCT Type of publication: journal publication Setting: inpatient Recruitment dates: 19 February 2020-31 March 2020 Country: China Language: English Number of centres: 7 Trial registration number: NCT04273321 Date of trial registration: 15 February 2020
Participants	Age: median age • 57 years (IQR 49–67) in the intervention group; • 55 years (IQR 38–65) in the control group Gender • 21 male (48.8%) in the intervention group • 20 male (46.5%) in the control group Proportion of confirmed infections: PCR positivity inclusion criterion Ethnicity: not reported Number of participants (recruited/allocated/evaluated): • 213 • allocated: 43 in the intervention group and 43 in the control group

Tang 2021 *(Continued)*

- evaluted: 43 in the intervention group and 43 in the control group

Severity of condition according to study definition:

- COVID-19 pneumonia (confirmed by chest-CT)
- admitted to the general wards

Severity of condition according to WHO score: moderate to severe 4-6

Co-morbidities: COPD, asthma, hypertension, coronary heart disease, diabetes, chronic renal failure

Inclusion criteria

- Age > 18 years old
- Confirmed SARS CoV 2 infection
- Admitted in the general wards
- Able to sign informed consent

Exclusion criteria

- Severe immunosuppression (HIV infection, long-term use of immunosuppressive agents)
- Pregnant or lactation period women
- Glucocorticoids are needed for other diseases
- Unwilling or unable to participate or complete the study
- Participating in other study

Previous treatments: not reported

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses) • Type of corticosteroid: methylprednisolone • Dose: 1 mg/kg/day in 100 mL 0.9% NaCl for 7 days • Route of administration: intravenous Treatment details of control group (e.g dose, route of administration, number of doses) • 100 mL 0.9% NaCl IV and standard care Concomitant therapy (e.g. description of standard care): standard therapy of COVID-19: according to the Chinese Diagnosis and Treatment Plan for COVID-19 (trial version 6); antivirals: 67 (77.9%) of patients, antibiotics: 61 (70.9%) of patients Duration of follow-up: at least 14 days after randomisation or until hospital discharge Treatment cross-overs: none documented Compliance with assigned treatment: yes

Outcomes	Primary study outcome: clinical deterioration 14 days after randomisation
	Review outcomes: inpatient setting
	• All-cause mortality at day 21, or longest observation period: reported as in-hospital all-cause mortality (unclear follow-up interval)
	• Improvement of clinical status during observation period:
	  ◦ Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: not reported
	  ◦ Ventilator-free days and alive: not reported
	• Worsening of clinical status during observation period:
	  ◦ Need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): not reported
	• Need for dialysis (at up to 28 days): not reported

Tang 2021 *(Continued)*

- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: reported
- Serious adverse events: not reported
- Adverse events (any grade): reported
- Hospital-acquired infections: reported

Additional study outcomes

- Clinical deterioration 14 days after randomisation (defined as deterioration of clinical signs and symptoms, new pulmonary or extrapulmonary lesions, progress in chest CT, ICU admission or death)
- Clinical cure 14 days after randomisation (defined as improvement of clinical signs and symptoms of COVID-19 and no need of additional therapy)
- Time from randomisation to clinical cure, median (IQR), days
- ICU admission

Identification	
Notes	Date of publication: 22 January 2021 Sponsor/funding: Beijing Chao Yang Hospital

Tomazini 2020

Study characteristics	
Methods	Trial design: multicenter, open-label RCT Type of publication: journal publication Setting: inpatient Recruitment dates: 17 April-23 June 2020 Country: Brazil Language: English Number of centres: 41 Trial registration number: NCT04327401 Date of trial registration: 31 March 2020

Participants	• Age: mean 60.1 years (SD 15.8) intervention group and 62.7 years (SD 13.1) control group
	• Gender: 90 (59.6%) male and 61 (40.4%) female in the intervention group; 97 (65.6%) male and 51 (34.5%) female in the control group
	• Proportion of PCR test results:
	  ○ Positive: 95.4% intervention arm, 95.9% control arm
	  ○ Negative: 0% intervention arm, 0.7% control arm
	  ○ Unclear: 4.6% intervention arm, 3.4% control arm
	• Ethnicity: not reported
	• Number of participants (recruited/allocated/evaluated): 545/151 intervention group and 148 control group/151 intervention group and 148 control group
	• Severity of condition according to study definition: all participants were mechanically ventilated
	• Severity of condition according to WHO score: severe 7-9
	• Co-morbidities: hypertension, diabetes, obesity, heart failure, chronic kidney failure

Tomazini 2020 *(Continued)*

- Inclusion criteria:
  - At least 18 years old
  - Confirmed or suspected COVID-19 infection
  - Receiving mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with partial pressure of arterial blood oxygen to fraction of inspired oxygen (PaO2:FIO2) ratio of 200 or less
- Exclusion criteria:
  - Pregnancy or active lactation
  - Known history of dexamethasone allergy
  - Corticosteroid use in the past 15 days for non-hospitalised patients
  - Use of corticosteroids during the present hospital stay for more than 1 day
  - Indication for corticosteroid use for other clinical conditions (eg, refractory septic shock)
  - Use of immunosuppressive drugs
  - Cytotoxic chemotherapy in the past 21 days
  - Neutropenia due to hematological or solid malignancies with bone marrow invasion
  - Consent refusal
  - Expected death in the next 24 hours
- Previous treatments: no

Interventions	Treatment details of intervention group (e.g dose, route of administration, number of doses): • Type of corticosteroid: dexamethasone • Dose: 20 mg once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge • Route of administration: intravenous Treatment details of control group (e.g dose, route of administration, number of doses): standard care Concomitant therapy (e.g description of standard care): hydroxychloroquine, azithromycin, other antibiotics, oseltamivir Duration of follow-up: 28 days Treatment cross-overs: no Compliance with assigned treatment • 25 deviations from protocol in the intervention arm (16.55%) • 1 patient received a corticosteroid other than dexamethasone • In the control arm, 52 patients received corticosteroids, of which 14 were protocol deviations (9.4%)

Outcomes	Primary study outcome: number of days alive and free from mechanical ventilation for at least 48 consecutive hours
	
	Review outcomes: Inpatient setting
	
	• All-cause mortality at day 21, or longest observation period: reported
	• Improvement of clinical status during observation period:
	  ◦ Liberation from IMV in participants i.e. transition to WHO ≤ 6 if ≥ 7 at baseline (see Figure 1). If liberation was not available directly, death was used as a proxy for assumed non-liberation counted together with participants alive and ventilated: reported
	  ◦ Ventilator-free days and alive: reported
	• Worsening of clinical status during observation period:
	  ◦ Need for IMV i.e. transition to WHO 7-9 if ≤ 6 at baseline (see Figure 1): reported
	• Need for dialysis (at up to 28 days): not reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at longest follow-up available: not reported

Tomazini 2020 *(Continued)*	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: not reported • Serious adverse events: reported • Adverse events (any grade): reported • Hospital-acquired infections: reported Additional study outcomes: Sequential Organ Failure Assessment (SOFA) scores
Identification	
Notes	Date of publication: 2 September 2020 Sponsor/funding: this trial was funded and supported by the Coalition COVID-19 Brazil. The Laboratórios Farmacêuticos provided the study drug, distribution logistics, and insurance for the study patients

AE: adverse event; **ARDS:** acute respiratory distress syndrome; **COPD:** chronic obstructive pulmonary disease; **CPK:** creatine phosphokinase; **CT:** computed tomography; **ECMO:** extracorporeal membrane oxygenation; **FiO2:** fraction of inspired oxygen **ICU:** intensive care unit; **IMV:** invasive mechanical ventilation; **IQR:** interquartile range: **IV:** intravenous; **LDH:** lactate dehydrogenase; **NIV:** non-invasive ventilation; **PaO2:** partial pressure of oxygen; **PEEP:** positive end-expiratory pressure; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SaO2:** arterial oxygen saturation; **SpO2:** blood oxygen saturation; **WHO:** World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
EUCTR2020-001445-39-ES	Corticosteroid plus other active substances versus standard care
EUCTR2020-001616-18-ES	Inhaled corticosteroids
EUCTR2020-001889-10	Inhaled corticosteroids
IRCT20120225009124N4	Corticosteroid plus other active substances versus standard care
IRCT20190312043030N2	Corticosteroid plus other active substances versus standard care
IRCT20200522047542N1	Topical corticosteroids
ISRCTN86534580	Inhaled corticosteroids
NCT04341038	Corticosteroid plus other active substances versus standard care
NCT04355637	Inhaled corticosteroids
NCT04359511	Withdrawn (competitor test RECOVERY)
NCT04361474	Topical corticosteroids
NCT04381364	Inhaled corticosteroids
NCT04411667	Corticosteroid plus other active substances versus standard care
NCT04416399	Inhaled corticosteroids
NCT04468646	Corticosteroid plus other active substances versus standard care

Study	Reason for exclusion
NCT04484493	Topical corticosteroids
NCT04534478	Corticosteroids for long-COVID treatment
NCT04551781	Corticosteroids for long-COVID treatment
NCT04561180	Corticosteroid plus other active substances versus standard care
NCT04569825	Topical corticosteroids
NCT04640168	Corticosteroid plus other active substances versus standard care
NCT04657484	Corticosteroids for long-COVID treatment
NCT04826822	Corticosteroid plus other active substance versus standard care

Characteristics of studies awaiting classification *[ordered by study ID]*

EUCTR2020-001307-16-ES

Methods	Trial design: open RCT Sample size: 104 Setting: inpatient Language: Spanish, English Number of centres: no information Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Diagnosis of SARS-CoV-2 by RT-PCR tested on a respiratory sample
	• Pneumonia confirmed by radiological imaging test
	• ARDS criteria:
	  ◦ bilateral infiltrates;
	  ◦ PO2/FiO2 < 300 mmHg
	  ◦ reasonable clinical exclusion of heart cause (requires all)
	  ◦ verbal consent of the patient
	Exclusion criteria
	• Age < 18 years
	• < 5 days from the onset of symptoms to randomisation
	• Pregnancy
	• Hypersensitivity or known allergy to methylprednisolone
	• Bacterial infection: not drained abscess, intravascular infection, bacterial pneumonia, septic shock, disseminated fungal infection
	• Participation in another trial in the previous 30 days
	• Acquired immunodeficiency syndrome
	• Previous use of corticosteroids (cumulative dose of prednisone (or equivalent) of > 300 mg in the last 21 days; or > 15 mg/d in the last 7 days before randomisation)
	• Cytotoxic treatment in the last 3 weeks

EUCTR2020-001307-16-ES *(Continued)*

	• Known or suspected adrenal insufficiency • Lung or bone marrow transplant • Severe liver disease
Interventions	Details of intervention: methylprednisolone • Dose: dosage unclear • Route of administration: IV Treatment details of control group (e.g dose, route of administration): no information Concomitant therapy: no information
Outcomes	Primary study outcome: death for any cause in the first 28 days after randomisation
Notes	Recruitment status: prematurely ended Prospective completion date: 6-month duration Date last update was posted: unclear Sponsor/funding: Fundación para la Investigación Biomédica Hospital Ramón y Cajal

EUCTR2020-001333-13-FR

Methods	Trial design: open RCT Sample size: 122 Setting: inpatient Language: French, English Number of centres: 18 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Patient aged > 18 • Patient affiliated to a health insurance plan • Patient who has given their free, informed and written consent or patient for whom an independent doctor has given their signed consent as part of an emergency procedure • Serum potassium > 3,5 mmol/L • Patient diagnosed COVID-positive by RT-PCR and/or scanner (patients admitted with already IMV and sedation, or with acute respiratory failure evolving very quickly) Exclusion criteria • Patient under guardianship or curatorship • Patient with plausible alternate diagnosis • ARDS evolving for > 4 days • Contraindication to hydroxychloroquine • Contraindication to dexamethasone • Uncontrolled septic shock • Untreated active infection or treated < 24 h • Long-term patient treated with corticosteroids (> 20 mg/d) or hydroxychloroquine • Immunocompromised patients: AIDS, bone marrow or solid organ transplant recipients

EUCTR2020-001333-13-FR *(Continued)*

	• Pregnant women
Interventions	Details of intervention • Dose: 20 mg dexamethasone + hydroxychloroquine • Route of administration: dexamethasone IV, hydroxychloroquine orally • Treatment details of control group (e.g dose, route of administration): hydroxychloroquine Concomitant therapy: no information
Outcomes	Primary study outcome: mortality on day 28
Notes	Recruitment status: prematurely ended Date of the global end of the trial: 7 August 2020 Date last update was posted: unclear Sponsor/funding: Groupe Hospitalier Paris Saint-Joseph

EUCTR2020-001553-48-FR

Methods	Trial design: open RCT Sample size: 304 Setting: inpatient Language: French Number of centres: 17 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age ≥ 18 years old • Hospitalisation for COVID-19 infection confirmed by RT-PCR or other virological method • SpO2 ≤ 94% in ambient air measured twice at 5-15 min intervals, or PaO2/FiO2 < 300 mmHg • Abnormalities on the chest X-ray or CT scan suggesting viral pneumonia • Signature of a free and informed consent by the patient Exclusion criteria • COVID-19 infection with first symptoms > 9 days ago (depending on the patient's questioning; the day of symptoms is defined as the first day with fever, cough, shortness of breath, and/or chills related to the COVID-19 infection) • Patients with primary or secondary immunodeficiency, including: HIV, chronic haematological disease, solid organ transplant, ongoing immunosuppressive treatment • Long-term corticosteroid therapy defined by taking > 10 mg/d (prednisone equivalent) • Infection suspected or confirmed or with bacteria, fungal agents, or viruses (in addition to COVID-19) • Known contraindication to systemic corticosteroids • Systolic blood pressure < 80 mmHg • SpO2 < 90% under 5 L/min of oxygen in the mask at medium concentration, or higher oxygen requirements • Patient on long-term oxygen therapy • Mechanical ventilation in progress

EUCTR2020-001553-48-FR *(Continued)*

	• Septic shock in progress • Multi-organ failure in progress • Pregnant or breastfeeding woman (oral diagnosis) • Lack of affiliation or beneficiary of a Social Security scheme, - Guardianship, curatorship or safe-guard of justice
Interventions	Details of intervention • Dose: prednisone 0.75 mg (concrete dosage/time frame missing) • Route of administration: oral Treatment details of control group (e.g dose, route of administration): standard care Concomitant therapy: no information
Outcomes	Primary study outcome • Number of patients on day 7 of randomisation (i.e. on day 14 of symptoms ± 5 days) presenting a theoretical indication for transfer to ICU with a respiratory indication evaluated by an SpO2 < 90% stabilised at rest and under 5 L/min of oxygen at mask at medium concentration measured twice 5-15 min apart. The average value of the two measurements will be used.
Notes	Recruitment status: prematurely ended Prospective completion date: 7 month predicted Date last update was posted: unclear Sponsor/funding: Hospices Civils de Lyon

IRCT20081027001411N3

Methods	Trial design: single-blinded RCT Sample size: 60 Setting: inpatient Language: English Number of centres: 4 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • COVID-19 patient with ARDS • Confirmed by positive PCR test for SARS-CoV-2 or confirmed by abnormal CT scan finding (bilateral, subpleural, peripheral ground glass opacities) • SpO2 < 93% • Not responding to standard COVID-19 treatment after 48-72 h Exclusion criteria • Type I diabetes • Asthma and lung diseases • Malignancies • Kidney and heart failure • Uncontrolled high blood pressure

IRCT20081027001411N3 *(Continued)*

- Positive pro-calcitonin and active infection
- Taking immunosuppressive drugs and corticosteroids
- Pregnant or lactating women
- Prescribed antibiotics due to a bacterial infection

Interventions	Details of intervention • Dose: 0.5 mg/kg prednisolone in 3 divided doses up to 30 mg/d for 5-7 days • Route of administration: not stated Treatment details of control group (e.g dose, route of administration): control group receives standard treatment for COVID-19 disease Concomitant therapy: not stated
Outcomes	Primary study outcome • Radiographic features findings (CT scan day 8+14) • Mortality rate • O2 saturation (day 8 + 14) • Need for an oxygen therapy
Notes	Recruitment status: completed Prospective completion date: 30 June 2020 Date last update was posted: 1 June 2020 Sponsor/funding: Teheran University of Medical Sciences

IRCT20100228003449N31

Methods	Trial design: open-label, randomised clinical trial Sample size: 119 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Adult patients (18-85 years old) • With diagnosis of COVID-19 according to laboratory, clinical or radiological findings • With indication for hospitalisation Exclusion criteria • Contraindication of corticosteroids (uncontrolled diabetes mellitus, active bacteria, fungal or parasite infections, hypersensitivity reactions, close angle glaucoma, uncontrolled neuropsychiatric disorders, unstable cardiovascular disorders including acute myocardial infarction, acute thrombosis, uncontrolled hypertension, viral hepatitis, history of corticosteroids induced myopathy) • Pregnancy lactation • History of recent corticosteroids

IRCT20100228003449N31 *(Continued)*

	• Other immunosuppressant drugs use
Interventions	3 groups comparing different doses of dexamethasone Details of intervention: • Type of corticosteroids: dexamethasone • Dose: 4 mg twice a day for 7-10 days • Route of administration: IV Treatment details of control groups (e.g dose, route of administration) • 8 mg twice a day for 7-10 days • 8 mg ≥ 3 times a day for 7-10 days Concomitant therapy: no
Outcomes	Primary study outcome • Improvement of patients' chief complaint • Improvement in peripheral SpO2 • Decrease in serum CRP, hyperglycaemia, changes in mood, myopathy, secondary infections
Notes	Recruitment status: completed Prospective completion date: no information Date last update was posted: 8 October 2020 Sponsor/funding: Teheran University of Medical Sciences

IRCT20120215009014N354

Methods	Trial design: double- blind, phase II RCT Sample size: 81 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age 18-70 years • Hospitalised in ICU < past 48 h • Mild to moderate ARDS due to COVID-19 • Bilateral pulmonary infiltration in chest X-ray or CT-scan • Respiratory distress with > 24 breaths/min Exclusion criteria • Pregnancy or breastfeeding • Cardiopulmonary oedema • Severe acute respiratory distress syndrome • Using antioxidant drugs

IRCT20120215009014N354 *(Continued)*

- Chronic liver or renal disease
- Contraindication of N-acetyl cysteine

Interventions	Details of intervention group 1 • Type of corticosteroid: hydrocortisone • Dose: 50 mg every 6 h for 5 days • Route of administration: IV Details of intervention group 2 • Type of corticosteroid: methylprednisolone • Dose: 40 mg every 12 h for 5 days • Route of administration: IV Details of intervention group 3 • Type of corticosteroid: dexamethasone • Dose: 20 mg daily for 5 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): Concomitant therapy: routine care
Outcomes	Primary study outcome • Need for mechanical ventilation (at day 28) • Patients' clinical status (at day 28) • Mortality (at day 28)
Notes	Recruitment status: completed Prospective completion date: 5 August 2020 Date last update was posted: 1 May 2020 Sponsor/funding: Hamedan University of Medical Sciences

IRCT20160118026097N4

Methods	Trial design: unblinded, RCT Sample size: 60 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age between 18 and 70 years • Laboratory confirmation of COVID-19 infection with RT-PCR from any diagnostic sampling source

IRCT20160118026097N4 *(Continued)*

- New organ dysfunction, which is related to COVID-19, includes:
  - hypoxia requires supplemental oxygen to maintain oxygen saturation > 90%
  - hypotension (systolic blood pressure < 90 mmHg) or need for vasopressor/inotropic drug.
  - renal impairment (especially creatinine) 50% of baseline, onset, received based on glomerular filtration film.
- Reduce the Glasgow scale by ≥ 2
- Thrombocytopenia (< 150,000 platelets per millimetre)
- Symptoms of gastrointestinal upset requiring hospitalisation (eg, severe nausea, vomiting, diarrhea, or abdominal pain)

Exclusion criteria

- Sensitivity or sensitivity to lopinavir/ritonavir or recombinant IFN-β1b, including toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema or angioedema syndrome
- ALT above 5 times normal
- Use of drugs that are contraindicated with lopinavir/ritonavir and do not replace or stop during the study period, such as CYP3A inhibitors
- Pregnancy - eligible female participants are tested at gestational age before enrolling in a pregnancy study.
- HIV infection is known to cause concern about the resistance to lopinavir/ritonavir if used in combination with other anti-HIV drugs
- Uncontrolled diabetes (prohibition of prednisolone)
- According to the 31st National Guide, all vulnerable groups, such as the mentally disabled, emergency patients, or inmates, are excluded from the study

Interventions	Details of intervention • Type of corticosteroids: dexamethasone • Dose: daily dexamethasone dose of 0.1 mg/kg body weight (our plausible correction from *"dexamethasone is treated daily 0/1mg/kg for a week"* as stated in the trial register) • Route of administration: no information Treatment details of control group (e.g dose, route of administration): treatment according to Ministry of Health's protocol Concomitant therapy: no information
Outcomes	Primary study outcome: mortality rate or recovery within 30 days after hospitalisation
Notes	Recruitment status: completed Prospective completion date: no information Date last update was posted: 13 September 2020 Sponsor/funding: Ghoum University of Medical Sciences

IRCT20200611047727N3

Methods	Trial design: single blinded, RCT Sample size: 60 Setting: inpatient Language: English Number of centres: 1

IRCT20200611047727N3 *(Continued)*

	Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Oxygen saturation level < 93 • At least 7 days have passed since the onset of symptoms • At least 5 days of antiviral treatment Exclusion criteria • Patients who are unable to go for follow-up scans
Interventions	Details of intervention: • Type of corticosteroids: methylprednisolone • Dose: 0.75-1 mg/kg for 5 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): standard care Concomitant therapy: no
Outcomes	Primary study outcome: radiological changes (before the intervention and 6 weeks later)
Notes	Recruitment status: completed Prospective completion date: no information Date last update was posted: 3 January 2021 Sponsor/funding: Shahid Beheshti University of Medical Sciences

IRCT20201015049030N1

Methods	Trial design: single-blind, RCT Sample size: 200 Setting: outpatient Language: English Number of centres: 4 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • COVID-19 confirmed by positive PCR test for SARS-CoV-2 or confirmed by abnormal CT scan finding (bilateral, subpleural, peripheral ground glass opacities) • SpO2 between 90%-95% • Patients with severe respiratory symptoms such as cough, shortness of breath and severe shortness of breath or CRP > 20 or after 3 days of standard treatment worsened symptoms of the disease, including exacerbated fevers, aggravated weakness or aggravated shortness of breath based on the physician's clinical judgment Exclusion criteria • Patients with a history of underlying disease such as diabetes, malignancies, renal and heart failure, uncontrolled hypertension

IRCT20201015049030N1 *(Continued)*

	• Patients taking immunosuppressive drugs and corticosteroids • Patients with other active infections • Pregnant or lactating women
Interventions	Details of intervention • Type of corticosteroids: dexamethasone • Dose: 8 mg (if patient's condition does not change, the dose will repeat after 48 h) • Route of administration: no information Treatment details of control group (e.g dose, route of administration): standard care Concomitant therapy: no
Outcomes	Primary study outcome • O2 saturation • Mortality rate • Need for an oxygen therapy • Constitutional (The review authors are unsure about the meaning of "Constitutional" and the study registry entry does not provide further information. The characteristics of this study will be updated once a publication is available.) • Needs of hospitalisation
Notes	Recruitment status: completed Prospective completion date: no information Date last update was posted: 7 November 2020 Sponsor/funding: Teheran University of Medical Sciences

ISRCTN33037282

Methods	Trial design: open-label, RCT Sample size: 680 Setting: inpatient Language: English Number of centres: 3 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Able to understand and sign the informed consent • SARS-CoV-2 positive on at least 1 upper respiratory swab or bronchoalveolar lavage • PaO2 ≤ 60 mmHg or SpO2 ≤ 90% or on HFNC, CPAP or NPPV at randomisation • Age ≥ 18 years old at randomisation Exclusion criteria • On IMV (either intubated or tracheostomised) • Heart failure as the main cause of acute respiratory failure • On long-term oxygen or home mechanical ventilation

ISRCTN33037282 *(Continued)*

	• Decompensated liver cirrhosis • Immunosuppression (i.e. cancer on treatment, post-organ transplantation, HIV-positive, on immunosuppressant therapy) • Chronic renal failure with dialysis dependence • Progressive neuro-muscular disorders • Cognitively impaired, dementia or decompensated psychiatric disorder • Quadriplegia/hemiplegia or quadriparesis/hemiparesis • Do-not-resuscitate order • Previous or current use of remdesivir • Participating in other clinical trial including experimental compound with proved or expected activity against SARS-CoV-2 infection • Any other condition that in the opinion of the investigator may significantly impact with patient's capability to comply with protocol intervention

Interventions	Details of intervention: per-protocol methylprednisolone administration and tapering
	• A. On day 1, loading dose of methylprednisolone 80 mg IV in 30 min, promptly followed by continuous infusion of methylprednisolone 80 mg/d in 240 mL of normal saline at 10 mL/h
	• B. From day 2 to day 8: infusion of methylprednisolone 80 mg/d in 240 mL of normal saline at 10 mL/h
	• C. From day 9 and beyond:
	  ○ If not intubated patient and PaO2/FiO2 > 200, taper to methylprednisolone 20 mg IV in 30 min 3/d for 3 days, then methylprednisolone 20 mg IV twice daily for 3 days, then methylprednisolone 20 mg IV once daily for 2 days, then switch to methylprednisolone 16 mg/d orally for 2 days, then methylprednisolone 8 mg/d orally for 2 days, then MP 4 mg/d orally for 2 days
	  ○ If intubated patient or PaO2/FiO2 ≤ 200 with at least 5 cm H2O CPAP, continue infusion of methylprednisolone 80 mg/d in 240 mL of normal saline at 10 mL/h until PaO2/FiO2 > 200 then taper as in A
	Treatment details of control group: per-protocol dexamethasone administration
	• A. dexamethasone 6 mg IV in 30 min or orally from day 1 to day 10 or until hospital discharge (if sooner)
	• B. After day 10 study treatment is interrupted
	Concomitant therapy: no

Outcomes	Primary study outcome
	• Recovery time measured in days using patient records
	• Recovery time determined as the time until hospital discharge when each of the following criteria were met:
	  ○ decrease in laboratory severity markers
	  ○ improvement in symptoms
	  ○ decrease in oxygen requirement until nasal cannula or supplementary oxygen removal and at least 2 doses of the respective treatment have been received

Notes	Recruitment status: completed Prospective completion date: 30 April 2021 Date last update was posted: 19 November 2020 Sponsor/funding: University of Trieste

Munch 2021

Methods	Trial design: quadruple blinded, multi-centre RCT Sample size: 1000 Setting: inpatient Language: English Number of centres: 14 Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	
	• Aged ≥ 18 years or above AND
	• Confirmed SARS-CoV-2 (COVID-19) requiring hospitalisation AND
	• Use of one of the following:
	  ○ IMV OR NIV or continuous use CPAP for hypoxia OR
	  ○ oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system
	
	Exclusion criteria
	
	• Use of systemic corticosteroids for any other indication than COVID-19
	• IMV for > 48 h
	• Invasive fungal infection
	• Fertile woman (< 60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG
	• Known hypersensitivity to hydrocortisone
	• A patient for whom the clinical team has decided not to use IMV
	• Previously randomised into the COVID STEROID trial
	• Informed consent not obtainable

Interventions	Details of intervention • Dose: hydrocortisone continuous infusion: 200 mg (104 mL) every 24 h, bolus injections: 50 mg (10 mL) every 6 h, total treatment duration: 7 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): • sodium chloride 9 mg/mL continuous infusion: 104 mL every 24 h, bolus injections: 10 mL every 6 h, total treatment duration: 7 days Concomitant therapy: no information
Outcomes	Primary study outcome: days alive without life support (i.e. IMV, circulatory support or renal replacement therapy) from randomisation to day 28
Notes	Recruitment status: active, not recruiting Prospective completion date: 8 June 2021 Date last update was posted: 9 March 2021 Sponsor/funding: Scandinavian Critical Care Trials Group

NCT03852537

Methods	Trial design: double-blinded RCT Sample size: 44 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Patients admitted to hospital with COVID-19 pneumonia (high suspicion or confirmed by positive SARS CoV-2 testing). • Acute respiratory failure SpO2/FiO2 < 315 (SpO2 < 90% on room air or < 97% on 2L NC) Exclusion criteria • Contraindications or unwilling to use steroids by patient or provider • Refractory septic shock defined as a requirement of norepinephrine dose or equivalent above > 0.1 microgram/kg/min or 2 or more vasopressors • Pre-admission chronic use of steroids or other immunosuppressive medications • Adrenal insufficiency • Comfort care • Leukopenia < 1000/mm or neutropenia < 500/mm (except if attributable to pneumonia) • HIV positive with a CD4 count < 100 • Recent or past history of bone marrow or solid organ transplantation • Suspected flare of interstitial lung disease (infectious and non-infectious) • Positive influenza testing or high suspicion for influenza
Interventions	Details of intervention • Dose: methylprednisolone will be administered based on CRP-guided protocol outlined under 'Biomarker-adjusted steroid dosing' • Route of administration: no information Treatment details of control group (e.g dose, route of administration): usual care as determined by the patients treatment team. Concomitant therapy: no information
Outcomes	Primary study outcome: fasibility of the timely initiation of corticosteroids and implementation of biomarker-titrated corticosteroid dosing: percentage of eligible patients adhered to the timely initiation (time frame: within 30 days of enrolment in study)
Notes	Recruitment status: completed Prospective completion date: 15 March 2021 Date last update was posted: 13 April 2021 Sponsor/funding: Mayo Clinic

NCT04244591

Methods	Trial design: randomised, open-label

NCT04244591 *(Continued)*

	Sample size: 80 Setting: inpatient Language: English Number of centres: multicenter Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria: • Adult • PCR confirmed COVID-19 infection • Symptoms developed > 7 days • PaO2/FiO2 < 200 mmHg • Positive pressure ventilation (non-invasive or invasive) or HFNC > 45 L/min for < 48 h • Requiring ICU admission Exclusion criteria • Pregnancy • Patients currently taking corticosteroids (cumulative 400 mg prednisone or equivalent) • Severe underlying disease, i.e. end stage of malignancy disease or end stage of pulmonary disease • Severe adverse events before ICU admission, i.e. cardiac arrest • Underlying disease requiring corticosteroids • Contraindication for corticosteroids • Recruited in other clinical intervention trial
Interventions	Details of intervention • Dose: methylprednisolone 40 mg every 12 h for 5 days • Route of administration: no information Treatment details of control group (e.g dose, route of administration): standard care Concomitant therapy: no information
Outcomes	Primary study outcome • Lower Murray lung injury score (time frame: 7 days after randomisation) • Lower Murray lung injury score (time frame: 14 days after randomisation)
Notes	Recruitment status: completed Prospective completion date: 13 April 2020 Date last update was posted: 13 April 2020 Sponsor/funding: Peking Union Medical College Hospital

NCT04325061

Methods	Trial design: open-label RCT Sample size: 19 Setting: inpatient

NCT04325061 *(Continued)*

	Language: English Number of centres: multicenter Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	
	• Age ≥ 18 years
	• Positive RT-PCR assay for COVID-19 in a respiratory tract sample
	• Intubated and mechanically ventilated
	• Acute onset of ARDS, as defined by Berlin criteria as moderate-to-severe ARDS, which includes:
	  ○ having pneumonia or worsening respiratory symptoms
	  ○ bilateral pulmonary infiltrates on chest imaging (X-ray or CT scan)
	  ○ absence of left atrial hypertension, pulmonary capillary wedge pressure < 18 mmHg, or no clinical signs of left heart failure
	  ○ hypoxaemia, as defined by a PaO2/FiO2 ratio of ≤ 200 mmHg on PEEP of ≥ 5 cm H2O, regardless of FiO2
	• Exclusion criteria
	  ○ Routine treatment with corticosteroids during the previous week irrespective of dose
	  ○ Corticosteroid use within the previous 24 h of > 20 mg of dexamethasone or equivalent
	  ○ Patients with a known contraindication to corticosteroids
	  ○ Decision by a physician that involvement in the study is not in the patient's best interest
	  ○ Pregnancy and breast-feeding
	  ○ Participation in another therapeutic trial

Interventions	Details of intervention • Dose: dexamethasone (20 mg/daily/from day 1 of randomisation for 5 days, followed by 10 mg/daily from day 6 to 10 of randomisation • Route of administration: IV Treatment details of control group (e.g dose, route of administration): patients will be treated with standard intensive care Concomitant therapy: no information
Outcomes	Primary study outcome: all-cause mortality at 60 days after enrolment
Notes	Recruitment status: terminated (lack of enrolment) Prospective completion date: June 2020 Date last update was posted: February 2021 Sponsor/funding: Dr. Negrin University Hospital

NCT04746430

Methods	Trial design: open-label RCT Sample size: 2000 Setting: outpatient Language: Dutch, English Number of centres: no information

NCT04746430 *(Continued)*

	Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Age ≥18 years
	• A positive test for SARS-CoV-2
	• GP consultation for deteriorating COVID-19 symptoms
	• Additional inclusion criteria in order to be eligible for randomisation to the trial:
	  ○ exercise-induced desaturation, defined as SpO2 < 92% (< 90% for COPD patients) and/or an absolute drop of ≥ 4% in SpO2 after a 1-min sit-to-stand test OR
	  ○ SpO2 < 92% (< 90% for COPD patients) at rest with GP's and patient's shared decision to keep patient at home despite this in itself being an indication for referral to hospital
	Exclusion criteria
	• Inability to understand and sign the written consent form
	• Inability to perform saturation measurements or sit-to-stand test
	• Not willing to be admitted to hospital
	• On the discretion of the recruiting clinician if he or she deems a patient not eligible
	• Contra-indication for dexamethasone

Interventions	Details of intervention: • Dose: 6 mg dexamethasone prescribed for 10 days and as a precaution combined with electronic monitoring of saturation and other signs and symptoms • Route of administration: most likely systemic Treatment details of control group (e.g dose, route of administration): only remote monitoring Concomitant therapy: no information
Outcomes	Primary outcome: time to first hospital admission or death (time frame: 28 days)
Notes	Recruitment status: terminated (too few patients) Prospective completion date: March 2022 Date last update was posted: 5 April 2021 Sponsor/funding: General Practitioners Research Institute

Rashad 2021

Methods	• Trial design: randomised, controlled, single blinded • Sample size: 69 • Setting: inpatient • Language: English • Number of centres: no information • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria:
	  ○ 18 years and older
	  ○ Respiratory rate > 30 cycle/minute, Bilateral CT infiltration > 30%, PaO2/FiO2 ratio <150 or saturation <90 on >6L/min, Two positive laboratory tests of: (CRP>100 g/dL, lymphocytes<600 / mm3, D dimer>L, Ferritin >500)

Rashad 2021 *(Continued)*

	• Exclusion criteria: ○ Pediatric patients < 18 years old, patients with active bacterial or fungal infection and patients who were not requiring supplemental oxygen

Interventions	• Details of intervention:
	  ○ Dose: dexamethasone pulse therapy
	  ○ Route of administration: no information
	• Treatment details of control group (e.g dose, route of administration): tocilizumab therapy
	• Concomitant therapy: no information

Outcomes	Primary study outcome: proportion of participants with Overall Survival at 14 days
Notes	Recruitment status: preprint published; unclear methodology; waiting for published fulltext Prospective completion date: August 2020 Date last update was posted: August 2020 Sponsor/funding: South Valley University

ALT: alanine transaminase; **ARDS:** acute respiratory distress syndrome; **COPD:** chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure; **CPK:** creatine phsphokinase; **CRP:** C-reactive protein; **CT:** computed tomography; **FiO2:** fraction of inspired oxygen; **HFNC:** high-flow nasal cannula; **ICU: i**ntensive care unit; **IMV:** invasive mechanical ventilation; **IQR:** interquartile range: **IV:** intravenous; **LDH:** lactate dehydrogenase; **NPPV:** non-invase positive pressure ventilation; **PaO2:** partial pressure of oxygen; **PEEP:** positive end-expiratory pressure; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SpO2:** blood oxygen saturation

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR2000029386

Study name	Effectiveness of glucocorticoid therapy in patients with severe coronavirus disease 2019: protocol of a randomised controlled trial
Methods	Trial design: open-label RCT Sample size: 48 Setting: inpatient Language: Chinese, English Number of centres: single centre Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Aged ≥ 18 years • Severe COVID-19 • Willing to give informed consent Exclusion criteria • Allergic or intolerant to any therapeutic drugs used in this study • Pregnant or lactating women • Presence of severe systemic illness that may affect the effectiveness or safety evaluation for this stud
Interventions	Details of intervention:

ChiCTR2000029386 *(Continued)*

	• Dose: methylprednisolone at a dose of 1-2 mg/kg/d for 3 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): no glucocorticoid use Concomitant therapy: no information
Outcomes	Primary study outcome • Change in sequential organ failure assessment (SOFA) at 3 days after randomisation • Clinical improvement rate
Starting date	No information
Contact information	Dr. Yao-Kai Chen, Division of Infectious Diseases, Chongqing Public Health Medical Center, Chongqing 400036, China E-Mail: yaokaichen@hotmail.com
Notes	Recruitment status: recruiting Prospective completion date: unclear Date last update was posted: 5 May 2020 Sponsor/funding: Chongqing Special Research Project for Prevention and Control of Novel Coronavirus Pneumonia

ChiCTR2000029656

Study name	A randomised, open-label study to evaluate the efficacy and safety of low-dose corticosteroids in hospitalised patients with novel coronavirus pneumonia (COVID-19)
Methods	Trial design: randomised, open-label Sample size: 100 Setting: inpatient Language: Chinese, English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Adults (defined as age ≥ 18 years) • Patients with new type of coronavirus infection confirmed by PCR/serum antibodies • The time interval between symptom onset and random enrolment is within 10 days. The onset of symptoms is mainly based on fever. If there is no fever, cough or other related symptoms can be used • Imaging-confirmed pneumonia • In the state of no oxygen at rest, the patient's SPO2 ≤ 94% or shortness of breath (breathing frequency ≥ 24) or oxygenation index ≤ 300mmHg. Exclusion criteria • Known to receive hormone therapy orally or intravenously • Hormone therapy is needed due to concomitant disease upon admission • Patients with diabetes are receiving oral medication or insulin therapy

ChiCTR2000029656 *(Continued)*

	• Known contraindications to dexamethasone or other excipients (such as refractory hypertension; epilepsy or delirium and glaucoma) • Known active gastrointestinal bleeding in the past 3 months • Known difficulties in correcting hypokalaemia • Known secondary bacterial or fungal infections • Known immunosuppressive status (such as chemotherapy/radiotherapy/HIV infection within 1 month after surgery) • The clinician thinks that participating in the trial may cause patient damage (such as severe lymphocyte reduction) • The patient may be transferred to a non-participating hospital within 72 h
Interventions	Details of intervention • Dose: standard treatment and methylprednisolone for injection (no dosage information) • Route of administration: IV Treatment details of control group (e.g dose, route of administration): standard treatment Concomitant therapy: no information
Outcomes	Primary study outcome • ECG • Chest imaging • Complications • Vital signs • NEWS2Score
Starting date	14 February 2020
Contact information	Ronghui Du, +86 15337110926, bluesearh006@sina.com
Notes	Recruitment status: not yet recruiting Prospective completion date: 14 April 2020 Date last update was posted: 12 February 2020 Sponsor/funding: Wuhan Pulmonary Hospital

ChiCTR2000030481

Study name	The clinical value of corticosteroid therapy timing in the treatment of novel coronavirus pneumonia (COVID-19): a prospective randomised controlled trial
Methods	• Trial design: open-label RCT • Sample size: 200 • Setting: no information, probably inpatient • Language: Chinese, English • Number of centres: 3 • Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Patients who are > 18 years

ChiCTR2000030481 *(Continued)*

	• Definitely diagnosed with COVID-19 (i.e. the diagnosis of 2019-nCoV-infected pneumonia patients was diagnosed according to the diagnostic criteria for novel coronavirus pneumonia diagnosis and treatment program (trial version 5) issued by the National Health and Health Commission on February 5, 2020.)
	
	Exclusion criteria
	
	• Patients who are allergic to corticosteroid
	• Patients who are diagnosed with adrenal insufficiency
	• Severe immunosuppression, one of the following:
	  ○ infection with HIV and CD4 cell count below 350 cells per microliter
	  ○ immunosuppressive therapy after solid organ transplantation
	  ○ neutropoenia (< 500 cells/microliter) and so on;
	• Patients with cystic fibrosis or active tuberculosis
	• Patients with gastrointestinal bleeding in the past 3 months
	• Incomplete clinical data
	• Participated in other clinical research
	• Patients who cannot understand and execute the survey plan
	• Patients who abandoned treatment

Interventions	Details of intervention • Group 1: early corticosteroid intervention group • Group 2: middle-late corticosteroid intervention group • Dosage and route of administration: no information, most likely systemic Treatment details of control group (e.g dose, route of administration): no corticosteroid Concomitant therapy: no information
Outcomes	Primary study outcome: the time of duration of COVID-19 nucleic acid RT-PCR test results of respiratory specimens (such as throat swabs) or blood specimens change to negative. Among secondary outcomes: 21-day all-cause mortality
Starting date	1 March 2020
Contact information	Chen Zhenshun, +86 13627288300, chzs1990@163.com
Notes	Recruitment status: recruiting Prospective completion date: 30 April 2020 Date last update was posted: 3 March 2020 Sponsor/funding: Science and Technology Department of Hubei Province

CTRI/2020/07/026608

Study name	A clinical trial to study the effects of two drugs methylprednisolone and dexamethasone in patients with severe COVID-19
Methods	Trial design: randomised, parallel group trial Sample size: 40 Setting: inpatient

CTRI/2020/07/026608 *(Continued)*

	Language: English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Aged 18-80 years • Men and women • Laboratory-confirmed COVID-19 cases with ARDS Exclusion criteria • Mild and moderate COVID-19 • Severe immunosuppression (HIV infection, long-term use of immunosuppressive agents) • Pregnant or lactating women • Patients already on steroids • Patients with high procalcitonin level
Interventions	Details of intervention: • Dose: methylprednisolone 1 mg/kg once a day for 3 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): injection dexamethasone 6 mg IV once a day for 3 days Concomitant therapy: no information
Outcomes	Primary study outcome • Difference in IL-6 level from baseline • Days to ventilator liberation • Length of hospital stay • In-hospital all-cause mortality
Starting date	27 July 2020
Contact information	Prof V R Mohan Rao , India, 9841210011, medicinehod@chettinadhealthcity.com
Notes	Recruitment status: not yet recruiting Prospective completion date: estimated duration of trial 3 months Date last update was posted: 15 July 2020 Sponsor/funding: Chettinad Hospital and Research Institute Kelambakkam, Dr Ananthakumar PK

CTRI/2020/10/028731

Study name	Higher vs. lower doses of steroids in patients with COVID-19
Methods	Trial design: randomised, parallel group trial Sample size: 1500 Setting: inpatient

CTRI/2020/10/028731 *(Continued)*

	Language: English Number of centres: 3 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Aged ≥ 18 years • Confirmed SARS-CoV-2(COVID-19) requiring hospitalisation and use of one of the following: ○ IMV or NIV or continuous use of CPAP for hypoxia or oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system Exclusion criteria • Use of systemic corticosteroids for other indications than COVID-19 in doses > 6 mg dexamethasone equivalents • Use of systemic corticosteroids for COVID-19 for ≥ 5 consecutive days • Invasive fungal infection • Active tuberculosis • Fertile women (< 60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG • Known hypersensitivity to dexamethasone • Previously randomised into the COVID STEROID 2 trial • Informed consent not obtainable
Interventions	Details of intervention: dexamethasone • Dose: 12 mg, up to 10 days from randomisation or until hospital discharge or death, frequency: once daily • Route of administration: IV Treatment details of control group (e.g dose, route of administration): dexamethasone 6 mg, IV, up to 10 days from randomisation or until hospital discharge or death, frequency: once daily Concomitant therapy: no
Outcomes	Primary outcome: days alive without life support (i.e. IMV, circulatory support or renal replacement therapy) from randomisation (day 28)
Starting date	1 November 2020
Contact information	Dr Vivekanand Jha; vjha@georgeinstitute.org.in
Notes	Recruitment status: recruiting Prospective completion date: estimated duration of trial 1 year Date last update was posted: no information Sponsor/funding: Professor Anders Perner, Senior Staff specialist and professor in Intensive Care Medicine Dept of Intensive Care, Rigshospitalet

CTRI/2020/12/029894

Study name	Comparing the effectiveness of dexamethasone versus methylprednisolone in patients with moderate COVID 19 - a randomised controlled trial
Methods	Trial design: open-label, RCT

CTRI/2020/12/029894 *(Continued)*

	Sample size: 50 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Hospitalised patients with moderate SARS-COV-2 infection laboratory confirmed by RT-PCR, (moderate COVID-19: SPO2 < 94% under room air and requiring supplemental oxygen for hypoxemia, respiratory rate 24-30/min, NLR > 5, CRP 50-100 mg/L, serum ferritin 600-1500 ng/mL, serum LDH 300-500 IU/L, D Dimer 0.5-1.0 mic/mL, IL-6 20-100 pg/mL, CT chest showing 25%-75% infiltrates) Exclusion criteria • Patients with mild and severe COVID pneumonia • Patients who are already on steroid treatment for any underlying condition • Patients already started on antivirals • Pregnant or lactating women • Any known contraindication to short-term corticosteroid like severe immunosuppression, HIV infection or any other immunosuppressant usage
Interventions	Details of intervention: dexamethasone • Dose: 6 mg/8 mg, 7 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): methylprednisolone 32 mg/60 mg intravenous, 6 days Concomitant therapy: no
Outcomes	Primary outcome: mortality during hospital stay (day 1-day 7)
Starting date	No information
Contact information	DR R Nivetha, Department of General Medicine 1st floor SRM Medical College Hospital and Research Centre SRM University Potheri Kattankulathur, India nivethamdr@gmail.com
Notes	Recruitment status: not yet recruiting Prospective completion date: estimated duration 6 months Date last update was posted: no information Sponsor/funding: SRM Medical College Hospital and Research Centre

CTRI/2020/12/030143

Study name	Evaluation of different steroid regimes in critically ill adult patients of COVID-19 admitted to intensive care units

CTRI/2020/12/030143 *(Continued)*

Methods	Trial design: Sample size: 500 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Confirmed COVID-19 infection with pulmonary involvement • Admitted to ICU within 14 days of onset of symptoms • Receiving invasive or non -invasive positive pressure ventilation or respiratory support through HFNC Exclusion criteria • Septicaemia, active malignancy or patient on immunosuppressive therapy within last 3 months • Uncontrolled hyperglycaemia • Clinically important gastrointestinal bleed • Pregnancy • History of hypersensitivity to steroid preparations
Interventions	Details of intervention: dexamethasone • Dose: 6 mg, frequency: once daily for 10 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): methylprednisolone, 1 to 2 mg/kg body weight, IV, frequency: daily for 10 days Concomitant therapy: no
Outcomes	Primary outcome: 28-day mortality
Starting date	No information
Contact information	Dr Sukhyanti Kerai, Maulana Azad Medical College New Delhi, India drsukhi25@gmail.com
Notes	Recruitment status: not yet recruiting Prospective completion date: estimated duration 6 months Date last update was posted: no information Sponsor/funding: Maulana Azad Medical College and associated Lok Nayak Hospital

EUCTR2020-001413-20-ES

Study name	Efficacy and safety of siltuximab vs. corticosteroids in hospitalised patients with COVID-19 pneumonia
Methods	Trial design: phase 2, randomised, open-label

EUCTR2020-001413-20-ES *(Continued)*

	Sample size: 100 Setting: inpatient Language: Spanish, English Number of centres: single-centre Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	
	• Age ≥ 18 years old
	• Hospitalised patient (or documentation of a hospitalisation plan if the patient is in an emergency department) with illness of > 5 days of duration with evidence of pneumonia by chest radiography/CT and meets at least 1 of the following requirements:
	  ○ non-critical patient with pneumonia in radiological progression
	  ○ patient with progressive respiratory failure at the last 24-48 h
	  ○ laboratory confirmed SARS-CoV-2 infection (by PCR) or other commercialised analysis or public health in any sample collected 4 days before the randomisation or COVID-19 criteria following the defined diagnostic criteria at that time in the center
	  ○ patient with a maximum O2 support of 35%
	  ○ willing and able to comply with the study-related procedures/evaluations
	  ○ women of childbearing potential should have a negative serum pregnancy test before enrolment in the study and must commit to using methods highly effective contraceptives (intrauterine device, bilateral tubal occlusion, vasectomised couple and sexual abstinence)
	  ○ Written informed consent. In case of inability of the patient to sign the informed consent, a verbal informed consent from the legal representative or family witness (or failing this, an impartial witness outside the investigator team) will be obtained by phone. When circumstances so allow, participants should sign the consent form. The confirmation of the verbal informed consent will be documented in a document as evidence that verbal consent has been obtained.
	
	Exclusion criteria
	
	• Patient who, in the investigator's opinion, is unlikely to survive > 48 h after inclusion in the study
	• Presence of any of the following abnormal analytical values at the time of the inclusion in the study:
	  ○ absolute neutrophil count (RAN) < 2000/mm3
	  ○ AST or ALT > 5 times the ULN
	  ○ platelets < 50,000/mm3
	• In active treatment with immunosuppressants or previous prolonged treatment (> 3 months) of oral corticosteroids for a disease not related to COVID-19 at a dose > 10 mg of prednisone or equivalent per day
	• Known active tuberculosis (TB) or known history of TB uncompleted treatment
	• Patients with active systemic bacterial and/or fungal infections
	• Participants who, at the investigator's discretion, are not eligible to participate, regardless of the reason, including medical or clinical conditions, or participants potentially at risk of not following study procedures
	• Patients who do not have entry criteria in the ICU
	• Pregnancy or lactation
	• Known hypersensitivity to siltuximab or to any of its excipients (histidine, histidine hydrochloride, polysorbate 80 and sucrose)

Interventions	Details of intervention: siltuximab • Dose: 11 mg/kg • Route of administration: intravenous

EUCTR2020-001413-20-ES *(Continued)*

	Treatment details of control group (e.g dose, route of administration): methylprednisolone 250 mg/kg Concomitant therapy: no information
Outcomes	Primary study outcome: proportion of patients requiring ICU admission at any time within the study period (time frame 29 days).
Starting date	No information
Contact information	Felipe García, +349322754002884, fgarcia@clinic.cat
Notes	Recruitment status: temporarily halted Prospective completion date: prospective duration of trial 45 days Date last update was posted: no information Sponsor/funding: Fundació Clínic per a la Recerca Biomèdica

EUCTR2020-001457-43-FR

Study name	Dexamethasone and oxygen support strategies in ICU patients with COVID-19 pneumonia
Methods	Trial design: double-blind (Phase III) RCT Sample size: 550 Setting: inpatient Language: French, English Number of centres: 12 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age ≥ 18 years • Admitted to ICU within 48 h • Confirmed or highly suspected COVID-19 infection • Acute hypoxemic respiratory failure (PaO2 < 70 mmHg or SpO2 < 90% on room air or tachypnea > 30/min or laboured breathing or respiratory distress; need for oxygen flow ≥ 6L/min) • Any treatment intended to treat the SARS-CoV-2 infection (either as a compassionate use or in the context of a clinical trial, i.e remdesivir, lopinavir/ritonavir, favipiravir, hydroxychloroquine and any other new drug with potential activity) Exclusion criteria • Moribund patient • Pregnancy or lactation • Long-term therapy with corticosteroids with dosage ≥ 0.5 mg/kg/d • Active bacterial, fungal or parasitic infection without treatment • Missing option of obtaining informed consent from patient or legal representative • Allergy or intolerance to dexamethasone or one of its derivatives For patients without mechanical ventilation other exclusion criteria are: • Anatomic factors that inhibit nasal cannulation

EUCTR2020-001457-43-FR *(Continued)*

	• Hypercapny (paCO2 ≥ 50 mmHg)
Interventions	Details of intervention: dexamethasone • Dose: 4 mg • Route of administration: IV Treatment details of control group (e.g dose, route of administration): placebo, IV Concomitant therapy: no information
Outcomes	Primary study outcome • Time-to-death from all causes within the first 60 days after randomisation • Time to need for mechanical ventilation (MV) (the additional objective is to assess whether oxygen support based on either HFNO or CPAP modality in COVID-19-related AHRF reduces the need for mechanical ventilation at day-28)
Starting date	No information
Contact information	fadila.amerali@aphp.fr
Notes	Recruitment status: ongoing Prospective completion date: October 2020 Date last update was posted: 2 April 2020 Sponsor/funding: APHP (An ancillary study CACAO (Covidicus air contamination) will be performed in 4 centers aiming at assessing the environmental contamination by SARS-CoV-2 according to the oxygen support modality. Additional funding will be searched for these analyses (submitted for ANR call)

EUCTR2020-001622-64-ES

Study name	Outpatient treatment of COVID-19 with early pulmonary corticosteroids as an opportunity to modify the course of the disease (TAC-COVID-19)
Methods	Trial design: open (phase IV) RCT Sample size: 200 Setting: outpatient Language: Spanish, English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age 18-75 • Both sexes • Diagnosis of SARS-CoV-2 infection, by PCR and/or Ac (IgM+) and/or Ag test • Clinical diagnosis of pulmonary involvement (respiratory symptoms +/- pathological auscultation +/- O2 desaturation) + Chest X-ray with mild-moderate or normal alterations • Verbal informed consent in front of witnesses, reflected in medical records

EUCTR2020-001622-64-ES *(Continued)*

	Exclusion criteria
	• Desaturation < 93% or PO2 < 62
	• Moderate-severe dyspnoea or significant respiratory or general deterioration that makes admission advisable
	• Chest X-ray with multifocal cotton infiltrates
	• Insulin-dependent diabetes with poor control or glycaemia in the emergency analysis > 300 mg/mL (fasting or not)
	• Other significant co-morbidities:
	  ○ severe renal failure CrCl < 30 mL/min
	  ○ cirrhosis or chronic liver disease
	  ○ poorly controlled hypertension
	  ○ heart rhythm disturbances (including prolonged QT).
	  ○ severe immunosuppression (HIV infection, long-term use of immunosuppressive agents); cancer.
	• Pregnant or lactating women
	• Use of glucocorticoids for other diseases
	• Unwilling or unable to participate until the study is complete
	• Participate in another study
	• Allergy or intolerance to any of the study drugs (prednisone, azithromycin or hydroxychloroquine)
	• Taking any of the drugs being tested within 7 days of being included in the study
	• Non-suppressible drugs with risk of QT prolongation or significant interactions

Interventions	Details of intervention: prednisone • Dose: concrete dosage/duration not mentioned • Route of administration: oral Treatment details of control group (e.g dose, route of administration): concomitant therapy Concomitant therapy: symptomatic treatment + hydroxychloroquine + azithromycin
Outcomes	Primary study outcome: the aim of this study is to explore the effectiveness and safety of oral corticosteroids (prednisone) in the treatment of early stage SARS-Cov-2 pneumonia in patients who do not yet meet hospital admission criteria: admission after 30 days.
Starting date	19 April 2020
Contact information	María Jesús Coma 0034610620180, mjcoma@hubu.es
Notes	Recruitment status: ongoing Prospective completion date: 3-month estimated duration of trial Date last update was posted: 20 April 2020 Sponsor/funding: Dra Ana Pueyo Bastida, Hospital Universitario de Burgos

EUCTR2020-001707-16-ES

Study name	Outpatient treatment of COVID-19 with early pulmonary corticosteroids as an opportunity to modify the course of the disease (TOCICOVID)
Methods	• Trial design: open (phase IV) RCT • Sample size: 60 • Setting: inpatient

EUCTR2020-001707-16-ES *(Continued)*

- Language: Spanish, English
- Number of centres: no information
- Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria • Patient > 18 years old • Ability to grant consent • Bilateral pneumonia caused by SARS-CoV-2 without response to the treatment used according to local protocol. This is defined as persistence of fever (above 37.5ºC without other focus) and respiratory worsening (more dyspnoea, more cough, oxygen therapy at increasing doses, worsening of the degree of respiratory distress according to the PaO2 / FiO2 ratio in categories “mild, moderate or serious ") or absence of improvement with respect to the previous state • Persistently elevated inflammatory markers, among which must be met: ferritin > 1000 ng/mL and/or D-dimer > 1500 ng / mL and/or IL-6 > 40 pg/mL Exclusion criteria • Pregnancy and lactation • Terminal situation or life expectancy < 30 days in the judgment of the researcher • Allergy or intolerance to any of the drugs under study or to any of the excipients of the preparations (eg polysorbate 80) • Non-tolerable interaction of the study drugs with some essential chronic medication of the patient • ALT/AST > 5 x ULN • Severe neutropenia (< 500 cells / mm3 • Plateletpenia < 50,000/mm3 • Sepsis (clinical suspicion of active infection at another level with a value on the qSOFA scale of ≥ 2 points) or septic shock (need for vasopressors to maintain a mean arterial pressure ≥ 65 mmHg with a lactate > 2 mmol/L, despite adequate volume replacement • Another active infection at any level • Complicated diverticulitis or intestinal perforation • Kidney failure with estimated glomerular filtration < 30 mL/min • Liver failure (Child B onwards) • Previous use (during the acute process or as chronic medication for another reason) of medication with potential effect in this phase of the disease (Janus kinase inhibitors, interleukin-1 inhibitors, other immunosuppressants or immunomodulators that, in the investigator's judgment could have an effect on the disease based on pathophysiological criteria or previous research or started up in this same period) • Be included in another clinical trial • Patients who, due to their current situation, their baseline situation or other aspects, in the opinion of the researcher, are not considered candidates to enter the study
Interventions	Details of intervention: tocilizumab • Dose: 20 mg/mL • Route of administration: IV Treatment details of control group (e.g dose, route of administration): methylprednisolone, 331 mg, IV Concomitant therapy: no information
Outcomes	Primary study outcome: respiratory situation at 24 hours, 3 and 7 days based on PaO2 / FiO2 ratio that graduates respiratory distress from mild (200-300), moderate (100-200) and severe (< 100). In addition, it will include: presence of dyspnea and grade according to the New York Health Association (NYHA) scale, presence of respiratory work and respiratory rate (FR)

EUCTR2020-001707-16-ES *(Continued)*

Starting date	22 July 2020
Contact information	IIS BIODONOSTIA 943006288
Notes	Recruitment status: ongoing Prospective completion date: 20-month estimated duration of trial Date last update was posted: 20 April 2020 Sponsor/funding: IIS BIODONOSTIA

EUCTR2020-001921-30

Study name	Steroids and unfractionated heparin in critically-ill patients with pneumonia from COVID-19 infection. A multicenter, interventional, randomised, three arms study design
Methods	Trial design: open RCT Sample size: 200 Setting: inpatient Language: Italian, English Number of centres: 9 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material) • Positive pressure ventilation (either non-invasive or invasive) from > 24 h • Invasive mechanical ventilation from < 96 h • P/F ratio < 150 • D-dimer level > 6 x upper limit of local reference range • PCR > 6 fold upper limit of local reference range Exclusion criteria • Age < 18 years • On-going treatment with anticoagulant drugs • Platelet count < 100.000/mmc • History of heparin-induced thrombocytopenia • Allergy to sodium enoxaparine or other LMWH, unfractionated heparin or methylprednisolone • Active bleeding or on-going clinical condition deemed at high risk of bleeding contraindicating anticoagulant treatment • Recent (in the last 1 month prior to randomisation) brain, spinal or ophthalmic surgery • Chronic intake of corticosteroids (we corrected *"Chronic assumption or oral corticosteroids"* as stated in the trial register by translating *"Assunzione cronica di corticosteroidi"*) • Pregnancy or breastfeeding or positive pregnancy test. In childbearing age women, before inclusion, a pregnancy test will be performed if not available • Clinical decision to withhold life-sustaining treatment or “too sick to benefit” • Presence of other severe diseases impairing life expectancy (e.g. patients are not expected to survive 28 days given their pre-existing medical condition) • Lack or withdrawal of informed consent

EUCTR2020-001921-30 *(Continued)*

Interventions	Details of intervention: methylprednisolone + unfractionated heparin (Eparina) • Dose: methylprednisolone (125-1000 mg/mL) + unfractionated heparin (Eparina) (25,000 international units) • Route of administration: IV Treatment details of control group (e.g dose, route of administration): heparin subcutaneous (25,000 international units) Concomitant therapy: no information
Outcomes	Primary study outcome: all-cause mortality at day 28
Starting date	14 May 2020
Contact information	Clinical Trials Quality Team, 0594225868, mighali.pasquale@aou.mo.it
Notes	Recruitment status: ongoing Prospective completion date: 1 year later, so May 2021 Date last update was posted: 26 June 2020 Sponsor/funding: AZIENDA OSPEDALIERO-UNIVERSITARIA POLICLINICO DI MODENA

EUCTR2020-002186-34-ES

Study name	Efficacy of the early use of corticotherapy in CoV-2 infection to prevent the progression of acute respiratory distress syndrome (ARDS) in COVID-19
Methods	Trial design: open-label, randomised trial Sample size: 100 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age 18-80 • Coronavirus-19 infection (SARS-CoV-2) demonstrated by nasopharyngeal smears PCR or any other biological sample; COVID-19 described as: nasopharyngeal smear with SARS-CoV-2 positive PCR, lung infiltrates by radiography (or other imaging technique) consistent with pneumonia, punctuation of 3 or 4 in the WHO Ordinal Scale for Clinical Improvement for COVID-19; one of the following criteria: ambient air oxygen, saturation> 90 and <94%, Pa: FiO2 (partial pressure O2 / fraction of inspired O2)> 200 and ≤300 mmHg, Sa: FiO2 (O2 saturation measured with pulse oximeter / inspired O2 fraction) ≤350 Exclusion criteria • Previous treatment with oral or IV corticosteroids for > 5 days in a row or alternate days (6 previous months) • Treatment during the previous 12 months with biological drugs such as monoclonal antibodies including anti-TNFα, anti-interleukins, Interferons type I

EUCTR2020-002186-34-ES *(Continued)*

	• Any other contraindication for the use of individualised corticosteroid pulses according to the clinical criteria of the patient medical team • Contraindications to treatment with methylprednisolone (limited to known hypersensitivity to the active substance and its excipients), as well as receiving treatment in a post-vaccination period (with live or live attenuated micro-organism vaccines) • Patients with severe ARDS, defined as SaFi < 150 • Patients with COPD requiring home oxygen
Interventions	Details of intervention: methylprednisolone • Dose: 250 mg; frequency not stated • Route of administration: IV Treatment details of control group (e.g dose, route of administration): standard care Concomitant therapy: no
Outcomes	Primary outcome: incidence of a combined variable made up of the variables death, ICU admission, non-IMV or need for high-flow oxygen therapy (defined as SaFi <200 with FiO2 ≥ 50%) (day 90)
Starting date	No information
Contact information	Ferran Martínez Valle, Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR)
Notes	Recruitment status: ongoing Prospective completion date: estimated duration 1 year Date last update was posted: no information Sponsor/funding: Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR)

EUCTR2020-003363-25-DK

Study name	Higher vs. lower doses of dexamethasone in patients with COVID-19 and severe hypoxia: the COVID STEROID 2 trial
Methods	Trial design: double-blinded RCT Sample size: 1000 Setting: inpatient Language: English Number of centres: 36 Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Aged ≥ 18 years or above AND
	• Confirmed SARS-CoV-2 (COVID-19) requiring hospitalisation AND
	• Use of one of the following:
	  ◦ IMV OR
	  ◦ NIV or continuous use of CPAP for hypoxia OR
	  ◦ oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system

EUCTR2020-003363-25-DK *(Continued)*

	Exclusion criteria • Use of systemic corticosteroids in doses > 6 mg dexamethasone equivalents for other indications than COVID-19 • Use of systemic corticosteroids for COVID-19 for ≥ 5 days or more • Invasive fungal infection • Active tuberculosis • Fertile woman (< 60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG • Known hypersensitivity to dexamethasone • Previously randomised into the COVID STEROID 2 trial • Informed consent not obtainable
Interventions	Details of intervention: • Dose: dexamethasone 12 mg (timeframe not mentioned) • Route of administration: IV Treatment details of control group (e.g dose, route of administration): dexamethasone 6 mg, IV Concomitant therapy: no information
Outcomes	Primary study outcome: days alive without life support (i.e.IMV, circulatory support or renal replacement therapy) from randomisation to day 28
Starting date	18 August 2020
Contact information	Department of intensive care, Ringshospitalet +4535457237, covid-steroid@cric.nu
Notes	Recruitment status: ongoing Prospective completion date: 18-month duration planned Date last update was posted: 18 August 2020 Sponsor/funding: Department of Intensive Care, Rigshospitalet, Novo Nordisk Foundation

EUCTR2020-004323-16

Study name	A randomised, multi-centre, double-blind study to evaluate the efficacy of high-dose administration of methylprednisolone in addition to standard treatment, in SARS-CoV2 (COVID-19) pneumonia patients
Methods	Trial design: randomised, multi-centre, double-blind study Sample size: 260 Setting: inpatient Language: Italian, English Number of centres: 5 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age = 18 years • Informed consent for participation in the study and for data processing

EUCTR2020-004323-16 *(Continued)*

- Molecular diagnosis with PCR test of Sars-CoV2 infection
- Hospitalisation in a specialist ward for CCOVID-19 patient care (e.g. Infectious Diseases, Pulmonology or Internal Medicine)
- Need for supplemental oxygen in any delivery mode with the exception of IMV
- PaO2/FiO2 between 100 and 300 mmHg
- Clinical/instrumental diagnosis (high-resolution chest CT scan or chest X-ray or lung ultrasound) of interstitial pneumonia for no more than 3 days
- Serum CRP > 5 mg/dL
- Interval from onset of SARS-CoV2 infection symptoms to randomiSation > 5 days

Exclusion criteria

- IMV
- Presence of shock or concomitant organ failure that requires admission to the ICU
- Pregnancy or breastfeeding
- Severe heart or kidney failure
- Known hypersensitivity to methylprednisolone, to dexamethasone or to an exception
- Diabetes not compensated according to the doctor's judgment
- Other clinical conditions that contraindicate methylprednisolone and cannot be treated or resolved according to the doctor's judgment
- Steroid bolus therapy in the week prior to enrolment for the study
- Enrolment in another clinical trial
- Patient already randomised in this study

Interventions	Details of intervention: • Dose: methylprednisolone (1 g/d for 3 days) • Route of administration: IV Treatment details of control group (e.g dose, route of administration): placebo, IV Concomitant therapy: no information
Outcomes	Primary study outcome: length of hospitalisation, calculated as the interval between randomisation and discharge from the hospital without the need for supplemental oxygen
Starting date	25 November 2020
Contact information	Massimo Costantini, 3355477208, massimo.costantini@ausl.re.it
Notes	Recruitment status: ongoing Prospective completion date: 4-month trial duration planned Date last update was posted: 25 November 2020 Sponsor/funding: AZIENDA OSPEDALIERA ARCISPEDALE SANTA MARIA NUOVA/IRCCS DI REGGIO EMILIA

NCT04329650

Study name	Efficacy and safety of siltuximab vs. corticosteroids in hospitalised patients with COVID-19 pneumonia
Methods	Trial design: phase 2, randomised, open-label

NCT04329650 *(Continued)*

	Sample size: 200 Setting: inpatient Language: Spanish, English Number of centres: 4 Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	
	• Age ≥ 18 years old
	• Hospitalised patient (or documentation of a hospitalisation plan if the patient is in an emergency department) with illness of > 5 days of duration with evidence of pneumonia by chest radiography/CT and meets at least 1 of the following requirements:
	  ○ non-critical patient with pneumonia in radiological progression and/or
	  ○ patient with progressive respiratory failure at the last 24-48 hours
	  ○ laboratory-confirmed SARS-CoV-2 infection (by PCR) or other commercialised analysis or public Health in any sample collected 4 days before the randomisation or COVID-19 criteria following the defined diagnostic criteria at that time in the centre
	  ○ Patient with a maximum O2 support of 35%
	  ○ Willing and able to comply with the study-related procedures/evaluations
	  ○ Women of childbearing potential should have a negative serum pregnancy test before enrolment in the study and must commit to using methods highly effective contraceptives (intrauterine device, bilateral tubal occlusion, vasectomised couple and sexual abstinence).
	  ○ Written informed consent. In case of inability of the patient to sign the informed consent, a verbal informed consent from the legal representative or family witness (or failing this, an impartial witness outside the investigator team) will be obtained by phone. When circumstances so allow, participants should sign the consent form. The confirmation of the verbal informed consent will be documented in a document as evidence that verbal consent has been obtained.
	
	Exclusion criteria
	
	• Patient who, in the investigator's opinion, is unlikely to survive > 48 h after the inclusion in the study.
	• Presence of any of the following abnormal analytical values at the time of the inclusion in the study:
	  ○ absolute neutrophil count < 2000/mm3
	  ○ AST or ALT > 5 times the upper limit of normality
	  ○ platelets < 50,000 per mm3.
	• In active treatment with immunosuppressants or previous prolonged treatment (> 3 months) of oral corticosteroids for a disease not related to COVID-19 at a dose > 10 mg of prednisone or equivalent per day.
	• Known active tuberculosis or known history of tuberculosis uncompleted treatment.
	• Patients with active systemic bacterial and/or fungal infections.
	• Patients who have received previous treatment with IL6 inhibitor (tocilizumab, sarilumab)
	• Participants who, at the investigator's discretion, are not eligible to participate, regardless of the reason, including medical or clinical conditions, or participants potentially at risk of not following study procedures
	• Patients who do not have entry criteria in the ICU.
	• Pregnancy or lactation
	• Known hypersensitivity to siltuximab or to any of its excipients (histidine, histidine hydrochloride, polysorbate 80 and sucrose)

Interventions	Details of intervention • Dose: single-dose of 11 mg/kg of siltuximab • Route of administration: IV

NCT04329650 *(Continued)*

	Treatment details of control group (e.g dose, route of administration) • A dose of 250 mg/24 h of methylprednisolone for 3 days followed by 30 mg/24 h for 3 days will be administered by IV infusion • If the patient is taking lopinavir/ritonavir, the dose will be 125 mg/ 24 h for 3 days followed by 15 mg/24 h for 3 days Concomitant therapy: no information
Outcomes	Primary study outcome: proportion of patients requiring ICU admission at any time within the study period (time frame: 29 days)
Starting date	
Contact information	Contact: Felipe García, MD+34932275400 ext 2884 NCT04329650, SILCOR-COVID-19, Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia" type="EXTERNAL">fgarcia@clinic.ca
Notes	Recruitment status: recruiting Prospective completion date: 20 May 2020 Date last update was posted: 17 April 2020 Sponsor/funding: Judit Pich Martínez

NCT04344730

Study name	Dexamethasone and oxygen support strategies in ICU patients with COVID-19 pneumonia (COV-IDICUS)
Methods	Trial design: quadruple-masked RCT Sample size: 550 Setting: inpatient Language: French, English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age ≥ 18 years • Admitted to ICU within 48 h • Confirmed or highly suspected COVID-19 infection • Acute hypoxaemic respiratory failure (PaO2 < 70 mmHg or SpO2 < 90% on room air or tachypnea > 30/min or laboured breathing or respiratory distress; need for oxygen flow ≥ 6 L/min) • Any treatment intended to treat the SARS-CoV-2 infection in the absence of contraindications (either as a compassionate use or in the context of a clinical trial, i.e remdesivir, lopinavir/ritonavir, favipiravir, hydroxychloroquine and any other new drug with potential activity). Exclusion criteria • Moribund status • Pregnancy or breastfeeding • Long term corticotherapy at a dose of 0.5mg/kg/j or higher

NCT04344730 *(Continued)*

	• Active and untreated bacterial, fungal or parasitic infection • Not Written informed consent from the patient or a legal representative if appropriate. If absence a legal representative the patient may be included in emergency procedure • hypersensitivity to dexamethasone or to any of the excipients • Not Affiliation to the French social security
Interventions	Details of intervention • Dose: dexamethasone 20 mg in 5 mL • Route of administration: IV Treatment details of control group (e.g dose, route of administration): placebo Concomitant therapy: study stratified according to subgroups (only oxygen therapy, CPAP, HFNC, IMV)
Outcomes	Primary study outcome • Time-to-death from all causes (time frame: day-60) • Time to need for mechanical ventilation (time frame: day-28) • Time-to-death from all causes within the first 60 days after randomisation
Starting date	10 April 2020
Contact information	Jean François TIMSIT, Pr
Notes	Recruitment status: active, not recruiting Prospective completion date: 31 December 2021 Date last update was posted: 9 February 2021 Sponsor/funding: Assistance Publique - Hôpitaux de Paris

NCT04345445

Study name	Study to evaluate the efficacy and safety of tocilizumab versus corticosteroids in hospitalised COVID-19 patients with high risk of progression
Methods	Trial design: open-label, randomised, cross-over interventional study Sample size: 310 Setting: inpatient Language: English Number of centres: 4 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Hospitalised symptomatic COVID-19 patients

NCT04345445 *(Continued)*

- Presence of clinical and radiological signs of progressive disease, AND laboratory evidence indicative of risk for cytokine storm complications:
  - Clinical: dyspnoea or respiratory rate > 20 breaths/min AND O2 saturation < 93% on room air or increasing need for O2 supplementation to maintain O2 saturation > 95% on room air WITH
  - Radiological: chest X-ray or CT indicative of pneumonia or worsening findings over time AND
  - Laboratory: CRP levels > 60 or an increase of CRP > 20 over 12 h WITH an increasing ferritin level or declining lymphocyte counts
- Age > 18 years
- Able to give consent

Exclusion criteria

- Known sensitivity/allergy to tocilizumab or other monoclonal antibodies
- AST/ALT > 5 times ULN
- Platelet counts < 50,000 or neutrophil counts < 500
- Active TB
- Pregnant
- Receipt of mechanical ventilation
- Has received other immunomodulatory drugs (including tocilizumab) in the past for the treatment of other conditions
- Individuals, in the opinion of the investigator, where progression to death is imminent and inevitable in the next 24 h irrespective of treatment provision or who have signed a do not resuscitate order.
- Participating in other clinical trials (subject to approval)
- Any serious medical condition or abnormal clinical laboratory tests which in the judgement of the investigator may compromise patient safety should he/she participate in the study

Interventions	Details of intervention • Dose: 8 mg/kg (body weight) tocilizumab • Route of administration: IV Treatment details of control group (e.g dose, route of administration): methylprednisolone 120 mg/day for 3 days IV Concomitant therapy: no information
Outcomes	Primary study outcome • The proportion of patients requiring mechanical ventilation (time frame: through study completion, and average of 6 months) • Mean days of ventilation (time frame: through study completion, and average of 6 months)
Starting date	14 April 2020
Contact information	Adeeba Kamarulzaman, MBBS+603-79492050 NCT04345445, TVCS-COVID19, Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalised COVID-19 Patients With High Risk of Progression" type="EXTERNAL">adeeba@um.edu.my
Notes	Recruitment status: not yet recruiting Prospective completion date: 31 October 2020 Date last update was posted: 14 April 2020 Sponsor/funding: University of Malaya

NCT04347980

Study name	Dexamethasone treatment for severe acute respiratory distress syndrome induced by COVID-19 (DHYSCO)
Methods	Trial design: single-blinded (participants) RCT Sample size: 122 Setting: inpatient Language: French, English Number of centres: multi-centre, no concrete information Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Patient > 18 years old
	• Patient affiliated to a health insurance plan
	• Patient who has given their free, informed and written consent or patient for whom an independent doctor has given their signed consent as part of an emergency procedure
	• Kaliemia > 3.5 mmol/L
	• Patient diagnosed COVID-19-positive by RT-PCR and/or CT
	• The diagnosis of COVID-19 will be made if:
	  ◦ patient with radiological images strongly suggestive of a chest scan associated with respiratory symptoms, without other obvious etiologies OR
	  ◦ patient with suggestive respiratory symptoms associated with a positive RT-PCR
	• Patients admitted to ICU with acute respiratory distress syndrome secondary to COVID-19, intubated for < 5 days with one of:
	  ◦ hypoxemia defined by PaO2/FiO2 ratio < 100 after 2 sessions of prone position
	  ◦ an alteration in pulmonary compliance (tidal volume divided by plateau pressure minus positive expiratory pressure) immediately or over the first 96 h after the start of ARDS defined by: immediately: impossibility of maintaining a plateau pressure < 30 cm of water in a ventilated patient with a tidal volume of 6 mL/kg of weight predicted by the size and a positive expiratory pressure at 10 cm of water, during the course of the evolution: decrease in compliance by 20% compared to the initial compliance (day of treatment of the intubated and ventilated patient) We define the start date of ARDS by the day and time when the patient is intubated and ventilated with regard to our definition of COVID-19
	Exclusion criteria
	• Patient under guardianship or curator
	• Patient with plausible alternate diagnosis
	• ARDS evolving for > 4 days
	• Contraindication to hydroxychloroquine: Known allergy or intolerance to the Hydroxychloroquine or to one of the excipients of the drug, in particular to lactose; documented QT prolongation and / or known risk factors for QT prolongation (including ongoing treatment with citalopram, escitalopram, hydroxyzine, domperidone or piperaquine), retinopathies
	• Contraindication to dexamethasone: known allergy or intolerance to dexamethasone or to one of the excipients of the drug, another evolving virosis (hepatitis, herpes, chickenpox, shingles), severe coagulation disorder
	• Uncontrolled septic shock
	• Untreated active infection or treated < 24 h
	• Long-term patient treated with corticosteroids (> 20 mg/day) or hydroxychloroquine
	• Immunocompromised patients: AIDS, bone marrow or solid organ transplant recipients
	• Pregnant women
	• Glucose-6-phosphate dehydrogenase (G6PD) deficiency

NCT04347980 *(Continued)*

Interventions	Details of intervention • Dose: dexamethasone (20 mg for 5 days followed by 10 mg for 5 days) combined with 600 mg/d dose of hydroxychloroquine for 10 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): 200 mg x 3/d enterally from J1 of the hydroxychloroquine for 10 days. If the patient is extubated before the 10th day, he will receive his last dose of hydroxychloroquine before. Concomitant therapy: no information
Outcomes	Primary study outcome: day-28 mortality
Starting date	April 2020
Contact information	Francois STEPHAN, MD, PhD33140948580 NCT04347980, 2037815010, Dexamethasone Treatment for Severe Acute Respiratory Distress Syndrome Induced by COVID-19" type="EXTERNAL">f.stephan@hml.fr
Notes	Recruitment status: recruiting Prospective completion date: August 2020 Date last update was posted: 17 April 2020 Sponsor/funding: Centre Chirurgical Marie Lannelongue

NCT04377503

Study name	Tocilizumab versus methylprednisolone in the cytokine release syndrome of patients with COVID-19
Methods	Trial design: phase II trial (open-label) RCT Sample size: 40 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Men and non-pregnant women > 18 years old
	• COVID diagnosis confirmed by RT-PCR
	• Pao2 / FIO2 < 200
	• Laboratory:
	  ○ high-sensitivity CRP > 5 mg /L
	  ○ LDH > 245 U/L
	  ○ ferritin > 300
	  ○ D-dimer > 1500
	  ○ IL-6 > 7.0 pg/mL
	Exclusion criteria

NCT04377503 *(Continued)*

	• Known sensitivity/allergy to tocilizumab • Active tuberculosis • Pregnancy • Individuals, in the opinion of the investigators where progression to death is imminent and inevitable in the next 24 h
Interventions	Details of intervention • Dose: tocilizumab, 8 mg/kg diluted in 100 mL of saline, dose will be repeated only once 12 h after the first dose • Route of administration: IV Treatment details of control group (e.g dose, route of administration): methylprednisolone at a dose of 1.5 mg/kg/d divided into 2 daily doses for 7 days. Then 1 mg/kg/day for another 7 days in 2 daily doses. Finally 0.5 mg/kg/d for another 7 days Concomitant therapy: no information
Outcomes	Primary outcome: patient clinical status 15 days after randomisation on a 7-category ordinal scale (time frame: 15 days after randomisation)
Starting date	No information
Contact information	Jose A Azevedo, MD, PhD+559832168110 NCT04377503, covid-19 hsd, Tocilizumab Versus Methylprednisolone in the Cytokine Release Syndrome of Patients With COVID-19" type="EXTERNAL">jrazevedo47@gmail.com
Notes	Recruitment status: not yet recruiting Prospective completion date: no information Date last update was posted: 6 May 020 Sponsor/funding: Hospital Sao Domingos

NCT04395105

Study name	Dexamethasone for COVID-19 related ARDS: a multicenter, randomised clinical trial
Methods	Trial design: multi-centre, open-label RCT Sample size: 284 Setting: inpatient Language: Spanish, English Number of centres: 3 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • ARDS according to Berlin's definition • PCR-confirmed COVID-19 • Length of mechanical ventilation ≤ 72 h Exclusion criteria

NCT04395105 *(Continued)*

	• Pregnancy • Terminal illness with very poor prognosis according to the investigator's judgement • Do-not-resucitate order • Known immunocompromised condition • Chronic use of systemic corticosteroids • Absence of informed consent • Active participation in other randomised clinical trial
Interventions	Details of intervention • Dose: dexamethasone 16 mg/d from day 1-5 followed by 8 mg/d from day 6-10 • Route of administration: IV Treatment details of control group (e.g dose, route of administration): usual treatment without using up to 6 mg /d of dexamethasone for 10 days Concomitant therapy: no information
Outcomes	Primary outcome • Days without ventilator support in the first 28 days following randomisation • Ventilator-free days at 28 days
Starting date	21 May 2020
Contact information	Contact: Pablo O Rodriguez, MD+541152990100 ext 4307 NCT04395105, 1264, Dexamethasone for COVID-19 Related ARDS: a Multicenter, Randomized Clinical Trial" type="EXTERNAL">prodriguez@cemic.edu.ar
Notes	Recruitment status: recruiting Prospective completion date: 31 January 2021 Date last update was posted: 20 July 2020 Sponsor/funding: Centro de Educación Medica e Investigaciones Clínicas Norberto Quirno

NCT04438980

Study name	Glucocorticoids in COVID-19 (CORTIVID)
Methods	Trial design: double-blinded RCT Sample size: 72 Setting: inpatient Language: Spanish, English Number of centres: 2 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age ≥ 18 years old • Diagnosis of SARS-CoV-2 pneumonia confirmed by RT-PCR on nasopharyngeal swab or sputum according to the recommendations of the Spanish Ministry of Health

NCT04438980 *(Continued)*

- Length of symptoms consistent with COVID-19 ≥ 7 days
- Hospital admission
- At least one of the following:
  - CRP > 60 mg/L
  - IL-6 > 40 pg/mL
  - ferritin > 1000 µg/L.
- Acceptance of informed consent

Exclusion criteria

- Allergy or contraindication to any of the drugs under study
- SpO2 < 90% (in air ambient) or PaO2 < 60 mmHg (in ambient air) or PaO2/FiO2 <300 mmHg
- Ongoing treatment with glucocorticoids, immunosuppressive, or biologic drugs with another indication
- Decompensated diabetes mellitus
- Uncontrolled hypertension
- Psychotic or manic disorder
- Active cancer
- Pregnancy or lactation
- Clinical or biochemical suspicion (procalcitonin > 0.5 ng/mL) of active infection other than SARS-CoV-2
- Out-of-hospital management patient
- Conservative or palliative management patient
- Participation in another clinical trial
- Any important and uncontrolled medical, psychological, psychiatric, geographic or social problem that contraindicates the patient's participation in the trial or that does not allow adequate follow-up and adherence to the protocol and evaluation of the study results.

Interventions	Details of intervention • Dose: methylprednisolone 120 mg/d for 3 days • Route of administration: IV • Treatment details of control group (e.g dose, route of administration): standard care and infusion bag of 100 mL of 0.9% saline • Concomitant therapy: no information
Outcomes	Primary outcome • Death • Need for admission in an ICU • Need for mechanical ventilation • Decrease in SpO2 < 90% (in ambient air) or PaO2 < 60 mmHg (in ambient air) or PaO2/FiO2 < 300 mmHg, associated with radiological impairment (time frame: at 14 days after randomisation)
Starting date	28 May 2020 recruitment start
Contact information	Iñigo Les Bujanda, PhD0034636346833 NCT04438980, CORTIVID, Glucocorticoids in COVID-19 (CORTIVID)" type="EXTERNAL">ilesbujanda@gmail.com
Notes	Recruitment status: recruiting Prospective completion date: February 2021 Date last update was posted: 22 July 2020 Sponsor/funding: Fundacion Miguel Servet

NCT04451174

Study name	Early use of corticosteroids in non-critical patients with COVID-19 pneumonia (PREDCOVID)
Methods	• Trial design: single-blinded (outcomes assessor) RCT • Sample size: 184 • Setting: inpatient • Language: Spanish, English • Number of centres: 1 • Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • ≥ 18 years • COVID-19 confirmed by PCR • Oxygen requirements until 35 % by venturi mask or 5 L/min by nasal cannula • Consent form signed Exclusion criteria • Previous steroid use ≥ 48 h • Pregnancy • Chronic respiratory failure • Requirements of mechanical ventilation (invasive or non-invasive) • Chronic liver damage Child Pugh B or C • Chronic kidney disease stage IV or V • Immunosuppressed • Participation on other trial
Interventions	Details of intervention • Dose: prednisone 40 mg days 1 to 4. Then, prednisone 20 mg days 5 to 8 • Route of administration: IV Treatment details of control group (e.g dose, route of administration): no intervention Concomitant therapy: no information
Outcomes	Primary outcome • Admission to ICU • Need for IMV or • All-cause death by day 28 • (Time frame: 28 days)
Starting date	23 June 2020
Contact information	Mauricio Salinas, MD+56 9 98254095 NCT04451174, 2092, Early Use of Corticosteroids in Non-critical Patients With COVID-19 Pneumonia" type="EXTERNAL">mrsalinas@uchile.cl
Notes	Recruitment status: recruiting Prospective completion date: 3 December 2020 Date last update was posted: 20 October 2020 Sponsor/funding: University of Chile

NCT04452565

Study name	NA-831, atazanavir and dexamethasone combination therapy for the treatment of COVID-19 infection (NATADEX)
Methods	• Trial design: phase 2/3, triple-blinded (care provider, investigator, outcomes assessor), RCT • Sample size: 525 • Setting: inpatient • Language: English • Number of centres: 31 • Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Hospitalisation for management of SARS CoV-2 infection
	• Positive SARS CoV-2 test
	• Age ≥ 18 years
	• Provision of informed consent
	• ECG ≤ 48 h prior to enrolment
	• Complete blood count, glucose-6 phosphate-dehydrogenase (G6PD), comprehensive metabolic panel and magnesium ≤ 48 h prior to enrolment from standard care.
	• If participating in sexual activity that could lead to pregnancy, individuals of reproductive potential who can become pregnant must agree to use contraception throughout the study. At least one of the following must be used throughout the study: Condom (male or female) with or without spermicide, Diaphragm or cervical cap with spermicide, Intrauterine device (IUD), Hormone-based contraceptive
	Exclusion criteria
	• Contraindication or allergy to NA-831, atazanavir, dexamethasone
	• Current use any antiviral drug or anti-inflammatory drug
	• Concurrent use of another investigational agent
	• IMV
	• Participants who have any severe and/or uncontrolled medical conditions such as:
	  ◦ unstable angina pectoris
	  ◦ symptomatic congestive heart failure
	  ◦ myocardial infarction
	  ◦ cardiac arrhythmias or
	  ◦ known prolonged QTc > 470 men, > 480 women on ECG pulmonary insufficiency
	  ◦ epilepsy (interaction with chloroquine)
	• Prior retinal eye disease
	• Concurrent malignancy requiring chemotherapy
	• Known chronic kidney disease, eGFR < 10 or dialysis, G-6-PD deficiency, if unknown requires G6PD testing prior to enrolment
	• Known porphyria
	• Known myasthenia gravis
	• Currently pregnant or planning on getting pregnant while on study
	• Breast feeding
	• AST/ALT > 5 x ULN
	• Bilirubin > 5 x ULN
	• Magnesium < 1.4 mEq/L
	• Calcium < 8.4 mg/dL > 10.6 mg/dL
	• Potassium < 3.3 > 5.5 mEg/L

NCT04452565 *(Continued)*

Interventions	• Arm 1: NA-831 30 mg orally twice a day for 1 day, followed by 30 mg once day for 4 consecutive days (5 days in total). • Arm 2: NA-831 60 mg orally twice a day for 1 day, followed by 30 mg once a day for 4 consecutive days (5 days in total). The drug will be supplied in 30 mg capsule. AND atazanavir 400 mg orally twice a day for 1 day, followed by 200 mg daily for 4 consecutive days (5 days total) • Arm 3: NA-831 60 mg orally twice a day for 1 day, followed by 30 mg once a day for 4 consecutive days (5 days in total). AND dexamethasone 8 mg orally twice a day for 1 day, followed by 4 mg daily for 4 consecutive days (5 days total). • Arm 4: atazanavir 400 mg orally twice a day for 1 day, followed by 200 mg daily for 4 consecutive days (5 days total). AND dexamethasone 8 mg orally twice a day for 1 day, followed by 4 mg daily for 4 consecutive days (5 days total). The drug will be supplied in 4 mg tablets.
Outcomes	Primary outcome • Time (hours) from randomisation to recovery defined as ◦ 1) absence of fever, as defined as at least 48 h since last temperature ≥ 38.0 °C without the use of fever-reducing medications AND ◦ 2) absence of symptoms of > mild severity for 24 h AND ◦ 3) not requiring supplemental oxygen beyond pre-COVID baseline AND ◦ 4) freedom from mechanical ventilation or death (time frame: 36 days)
Starting date	First Posted: 30 June 2020
Contact information	Brian Tran, MD1-415-941-3133 NCT04452565, NATADEX, NA-831, Atazanavir and Dexamethasone Combination Therapy for the Treatment of COVID-19 Infection" type="EXTERNAL">BTran@neuroactiva.com
Notes	Recruitment status: recruiting Prospective completion date: 15 February 2021 Date last update was posted: 7 September 2020 Sponsor/funding: NeuroActiva, Inc.

NCT04485429

Study name	Efficacy assessment of methylprednisolone and heparin in patients with COVID-19 pneumonia
Methods	Trial design: open-label RCT Sample size: 268 Setting: inpatient Language: English Number of centres: 1 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Confirmed diagnosis of COVID-19 by RT-PCR or serology with presence of IgM positive antibodies • Lung image (X-ray or chest CT) with involvement of at least 25% of the parenchyma • O2 saturation in ambient air ≤ 93%

NCT04485429 *(Continued)*

	• Alteration of inflammatory tests: D-Dimer above the reference value and Elevation of CRP, ferritin or LDH • Sign the consent form Exclusion criteria • QT interval prolongation • Imminence of orotracheal intubation (intubation prediction in the first 4 h after randomisation) • Women who are pregnant or breastfeeding • Corticosteroid allergy or intolerance • Chronic corticosteroid users (prednisone equivalent > 10 mg daily) • Patients diagnosed with cancer with increased bleeding potential • Patients in haemodialysis • History of peptic ulcer • Herpes zoster infection • History or active treatment of tuberculosis • Systemic fungal infection • Use of anticoagulation due to previous pathology • Glaucoma • Live virus vaccine up to 90 days before randomisation • Known coagulopathy or thrombocytopenia (< 40,000/mm3) or hypofibrinogenemia (< 50 mg/dL) • Recent bleeding • Another limiting comorbidity for administering the therapies provided for in this protocol in in researcher's opinion
Interventions	• Arm 1: methylprednisolone 0.5 mg/kg every 12 h IV for the first 14 days; followed by 0.5 mg/kg/day from day 15-21; followed by 0.25 mg/kg/day from day 22-25; followed by 0.125 mg/kg/day, from day 26-28 of treatment • Arm 2: enoxaparin 1 mg/kg SC every 12 h (if creatinine clearance > 40 mL/min) or unfractionated heparin dosed to target activated partial thromboplastin time (aPTT) between 1.5-2.0 times the normal value (if creatinine clearance ≤ 40 mL/min). The treatment period with full-dose heparin will be 7 days. After 7 days of full-dose heparin, participants will continue using prophylactic dose of heparin, according to the standard treatment routine • Arm 3: methylprednisolone + full-dose heparin (dosing see above) • Arm 4: standard care only
Outcomes	Primary outcome: rate of IMV (time Frame: 28 days)
Starting date	
Contact information	Eduardo M Rego, MD, PhD55 16 981110090 NCT04485429, 31180820600005249, Efficacy Assessment of Methylprednisolone and Heparin in Patients With COVID-19 Pneumonia" type="EXTERNAL">e-dumrego@hotmail.com
Notes	Recruitment status: recruiting Prospective completion date: 13 December 2020 Date last update was posted: 24 July 2020 Sponsor/funding: D'Or Institute for Research and Education

NCT04499313

Study name	Dexamethasone versus methylprednisolone for the treatment of patients with ARDS caused by COVID-19
Methods	• Trial design: open-label RCT • Sample size: 60 • Setting: inpatient • Language: English • Number of centres: 2 • Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Moderate to severe COVID-19 requires hospitalisation • SARS-CoV-2 infection will be confirmed by RT PCR/CT chest in every case Exclusion criteria • Participants with uncontrolled clinical status who were hospitalised from before • Contraindication/possible drug interaction • Participants who have any severe and/or uncontrolled medical conditions like, severe ischemic heart disease, epilepsy, malignancy, pulmonary/renal/hepatic disease, pregnancy, corpulmonale, etc
Interventions	Details of intervention: • Dose: dexamethasone (20 mg/daily/from day 1 of randomisation, followed by a tapering dose according to the patient's condition • Route of administration: IV Treatment details of control group (e.g dose, route of administration): methylprednisolone sodium succinate at a dose of 0.5 mg/kg (injectable solution) Concomitant therapy: no information
Outcomes	Primary outcome • The number of participants with 'clinical improvement' determined by the improvement of individual presenting symptoms of COVID19 • Changes in radiological and laboratory values • Patient admitted in general bed requiring High Dependency Unit (HDU), and an HDU patient requiring ventilator or intensive care support. • Mortality rate (In hospital) (time frame: following randomisation 30 days) • Clinical improvement (time frame: following randomisation 30 days)
Starting date	2 August 2020
Contact information	Abu Taiub Mohammed Mohiuddin Chowdhury, MBBS, MD008801817711079 NCT04499313, 10000753, Dexamethasone Vs Methylprednisolone for the Treatment of Patients With ARDS Caused by COVID-19" type="EXTERNAL">dr_mohiuddinchy@yahoo.com
Notes	Recruitment status: recruiting Prospective completion date: 30 November 2020 Date last update was posted: 18 August 2020 Sponsor/funding: Chattogram General Hospital

NCT04509973

Study name	Higher vs. lower doses of dexamethasone for COVID-19 and severe hypoxia (COVIDSTEROID2)
Methods	Trial design: quadruple-blinded, multi-centre, clinical RCT Sample size: 1000 Setting: inpatient Language: Swedish, Danish, English Number of centres: 53 Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Aged ≥ 18 years AND
	• Confirmed SARS-CoV-2 (COVID-19) requiring hospitalisation AND
	• Use of one of the following:
	  ○ IMV OR
	  ○ NIV or continuous use of continuous positive airway pressure (CPAP) for hypoxia OR
	  ○ Oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system
	Exclusion criteria
	• Use of systemic corticosteroids for other indications than COVID-19 in doses > 6 mg dexamethasone equivalents
	• Use of systemic corticosteroids for COVID-19 for ≥ 5 consecutive days
	• Invasive fungal infection
	• Active tuberculosis
	• Fertile woman (< 60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG
	• Known hypersensitivity to dexamethasone
	• Previously randomised into the COVID STEROID 2 trial
	• Informed consent not obtainable

Interventions	Details of intervention • Dose: dexamethasone 12 mg once daily in addition to standard care for up to 10 days. We will allow the use of betamethasone 12 mg at sites, where dexamethasone is not available • Route of administration: IV Treatment details of control group (e.g dose, route of administration): dexamethasone 6 mg once daily in addition to standard care for up to 10 days. We will allow the use of betamethasone 6 mg at sites, where dexamethasone is not available. Concomitant therapy: no information
Outcomes	Primary outcome: days alive without life support (i.e. IMV, circulatory support or renal replacement therapy) from randomisation to day 28
Starting date	27 August 2020
Contact information	Anders Perner, MD, PhD, Professor+4535458333 NCT04509973, RH-ITA-009, Higher vs. Lower Doses of Dexamethasone for COVID-19 and Severe Hypoxia" type="EXTERNAL">anders.perner@region-h.dk

NCT04509973 *(Continued)*

Notes	Recruitment status: recruiting Prospective completion date: 17 February 2022 Date last update was posted: 1 September 2020 Sponsor/funding: Scandinavian Critical Care Trials Group

NCT04513184

Study name	Randomised clinical trial of intranasal dexamethasone as an adjuvant in patients with COVID-19
Methods	Trial design: multicenter, double-masked (participant, care provider), RCT Sample size: 60 Setting: inpatient Language: Spanish, English Number of centres: 3 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • 18 -75 years old • Positive diagnosis of SARS-CoV-2 by real-time RT-PCR in oropharyngeal sample ≥ 7 days after the start of the infection • Hospitalised patients with moderate to severe respiratory complications that have not received mechanical ventilation • Patients receiving standard therapy at the Hospital General de México Eduardo Liceaga • Signing of the informed consent form • Patients of both sexes (non-pregnant female) ≥ 18 years of age will be eligible if they have a positive diagnostic sample by RT-PCR, pneumonia confirmed by chest imaging and oxygen saturation (SaO2) < 93% at ambient air or PaO2: FiO2 at ≤ 300 mg Hg Exclusion criteria • Patients participating in another research protocol • Patients receiving oral or IV glucocorticoids • Immunosuppressed patients (including HIV infection) • Glaucoma patients • Patients with allergy to dexamethasone • Pregnant or lactating women • Concomitant autoimmune diseases • Refusal by the patient or family to participate in the study
Interventions	Details of intervention • Dose: 6 mg dexamethasone from day 1-10 after randomisation • Route of administration: IV Treatment details of control group (e.g dose, route of administration): nasal dexamethasone 0.12 mg/kg/daily for 3 days from day 1, followed by 0.06 mg/kg/daily from day 4-10 after randomisation Concomitant therapy: no information

NCT04513184 *(Continued)*

Outcomes	Primary outcome • Evaluation of the clinical status of patients after randomisation, defined as a 2-point improvement in the WHO 7-point Ordinal Scale • Time of clinical improvement (time frame: 10 days after randomisation)
Starting date	14 July 2020
Contact information	Graciela A Cárdenas-Hernández, PhD+525556063822 ext 2012 NCT04513184, DI/20/407/04/36, Randomized Clinical Trial of Intranasal Dexamethasone as an Adjuvant in Patients With COVID-19" type="EXTERNAL">gracielacardenas@yahoo.com.mx
Notes	Recruitment status: recruiting Prospective completion date: primary completion date 30 March 2021 estimated study completion date 31 July 2021 Date last update was posted: 12 November 2020 Sponsor/funding: Edda Sciutto Conde

NCT04528329

Study name	Anosmia and / or ageusia in COVID-19: timeline, treatment with early corticosteroid and recovery
Methods	Trial design: open-label RCT Sample size: 300 Setting: no information Language: Arabic, English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Any case with COVID-19 • Age ≥ 18 years • Mild to moderate severity Exclusion criteria • Diabetes • Any contra-indication for the interventional drug • Mentally disabled cases
Interventions	Details of intervention: • Dose: early use of dexamethasone as early as the laboratory confirmation of inflammation • Route of administration: no information Treatment details of control group (e.g dose, route of administration): dexamethasone is to be used lately upon the deterioration of cases Concomitant therapy: no information

NCT04528329 *(Continued)*

Outcomes	Time to recovery (time frame: 1-6 weeks) from anosmia and/or ageusia
Starting date	30 August 2020
Contact information	Emad R Issak, MD01272228989 NCT04528329, PR0013, Anosmia and / or Ageusia and Early Corticosteroid Use" type="EXTERNAL">dr.emad.r.h.issak@gmail.com
Notes	Recruitment status: recruiting Prospective completion date: 15 April 2021 Date last update was posted: 29 March 2021 Sponsor/funding: ClinAmygate

NCT04528888

Study name	Steroids and unfractionated heparin in critically ill patients with pneumonia from COVID-19 infection (STAUNCH-19)
Methods	Trial design: multicenter, national, interventional, randomised, open-label Sample size: 210 Setting: inpatient Language: Italian, English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material) • Positive pressure ventilation (either non-invasive or invasive) from > 24 h • IMV from < 96 h • P/F ratio < 150 • D-dimer level > 6 x upper limit of local reference range • PCR > 6 fold upper limit of local reference range Exclusion criteria • Age < 18 years • Ongoing treatment with anticoagulant drugs • Platelet count <100.000/mmc • History of heparin-induced thrombocytopenia • Allergy to sodium enoxaparine or other LMWH, unfractionated heparin or methylprednisolone • Active bleeding or ongoing clinical condition deemed at high risk of bleeding contraindicating anticoagulant treatment • Recent (in the last 1 month prior to randomisation) brain, spinal or ophthalmic surgery • Chronic intake of corticosteroids (we corrected *"Chronic assumption or oral corticosteroids"* as stated in the trial register by translating *"Assunzione cronica di corticosteroidi"*) • Pregnancy or breastfeeding or positive pregnancy test. In childbearing age women, before inclusion, a pregnancy test will be performed if not available • Clinical decision to withhold life-sustaining treatment or 'too sick to benefit'

NCT04528888 *(Continued)*

	• Presence of other severe diseases impairing life expectancy (e.g. patients are not expected to survive 28 days given their pre-existing medical condition) • Lack or withdrawal of informed consent
Interventions	• Arm 1: enoxaparin SC at standard prophylactic dose (i.e. 4000 UI once day, increased to 6000 UI once day for patients weighing > 90 kg), treatment administered daily up to ICU discharge, destination ward decides whether discontinued • Arm 2: enoxaparin SC at standard prophylactic dose (i.e. 4000 UI once day, increased to 6000 UI once day for patients weighing > 90 kg), treatment administered daily up to ICU discharge, destination ward decides whether discontinuated AND methylprednisolone IV initial bolus of 0.5 mg/kg followed by administration of 0.5 mg/kg 4 times daily for 7 days, 0.5 mg/kg 3 times daily from day 8-10, 0.5 mg/kg 2 times daily at days 11 and 12 and 0.5 mg/kg once daily at days 13 and 14 • Arm 3: methylprednisolone IV initial bolus of 0.5 mg/kg followed by administration of 0.5 mg/kg 4 times daily for 7 days, 0.5 mg/kg 3 times daily from day 8-10, 0.5 mg/kg 2 times daily at days 11 and 12 and 0.5 mg/kg once daily at days 13 and 14 AND unfractionated heparin IV at therapeutic doses. Infusion started at an infusion rate of 18 IU/kg/h and then modified to attain APTT ratio in the range 1.5-2.0. APTT will be periodically checked at intervals no longer than 12 h. Treatment with unfractionated heparin will be administered up to ICU discharge. After ICU discharge anticoagulant therapy may be interrupted or switched to prophylaxis with LMWH in the destination ward, on the clinical judgement of the attending physician.
Outcomes	Primary outcome: all-cause mortality at day 28, defined as the comparison of proportions of patients' death for any cause at day 28 from randomisation
Starting date	1 September 2020
Contact information	Massimo Girardis, PD0594225878 ext 0039 NCT04528888, Staunch-19-1.1-26-04-20, Steroids and Unfractionated Heparin in Critically Ill Patients With Pneumonia From COVID-19 Infection" type="EXTERNAL">massimo.girardis@unimore.it
Notes	Recruitment status: recruiting Prospective completion date: 30 July 2021 Date last update was posted: 27 August 2020 Sponsor/funding: Massimo Girardis, University of Modena and Reggio Emilia

NCT04530409

Study name	Timing of corticosteroids in COVID-19
Methods	Trial design: open-label RCT Sample size: 450 Setting: no information Language: Arabic, English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Any case with COVID-19 ≥ 18 years, mild and moderate severity Exclusion criteria

NCT04530409 *(Continued)*

	• Any contra-indication for the interventional drug • Mentally disabled cases
Interventions	Details of intervention • Dose: early use of dexamethasone as early as the laboratory confirmation of inflammation • Route of administration: most likely systemic Treatment details of control group (e.g dose, route of administration): dexamethasone is to be used upon the deterioration of cases Concomitant therapy: no information
Outcomes	Primary outcome • Deterioration in the clinical picture of cases that necessitate hospitalisation • Percentage of cases whose clinical status deteriorate to ARDS • Percentage of cases that will need hospitalisation (time frame: 1-2 weeks) • Percentage of cases that deteriorate to ARDS (time frame: 1-2 weeks)
Starting date	
Contact information	Emad R Issak, MD01272228989NCT04530409, PR0012, Timing of Corticosteroids in COVID-19" type="EXTERNAL">dr.emad.r.h.issak@gmail.com
Notes	Recruitment status: recruiting Prospective completion date: estimated primary completion date 1 April 2021; Estimated study completion date: 1 May 2021 Date last update was posted: 16 February 2021 Sponsor/funding: ClinAmygate

NCT04545242

Study name	Efficacy of dexamethasone in patients with acute hypoxemic respiratory failure caused by infections (DEXA-REFINE)
Methods	Trial design: multicenter, open-label, clinical RCT Sample size: 980 Setting: inpatient Language: English Number of centres: 40 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Patients with acute hypoxemic respiratory failure (including ARDS) caused by Infections (including COVID-19) • Age ≥ 18 years • Intubated and mechanically ventilated

NCT04545242 *(Continued)*

	• Acute onset of AHRF (as defined by a PaO2/FiO2 ≤ 300 mmHg during at least 6 h from diagnosis. For the measurement of PaO2 and calculation of PaO2/FiO2 ratio, the minimum accepted value for PEEP is 5 cmH2O and for FiO2 is 0.3. ARDS is defined by Berlin criteria 4, which includes:
	  ○ (i) having pneumonia or worsening respiratory symptoms
	  ○ (ii) bilateral pulmonary infiltrates on chest imaging (X-ray or CT scan)
	  ○ (iii) absence of left atrial hypertension or no clinical signs of left heart failure, and
	  ○ (iv) hypoxaemia, as defined by a PaO2/FiO2 ≤ 300 mmHg on PEEP of ≥ 5 cmH2O, regardless of FiO2. Pulmonary or systemic infectious etiology of AHRF.
	
	Exclusion criteria
	
	• Patients with a known contraindication to corticosteroids
	• Patient included in another therapeutic clinical trial
	• Lack of informed consent

Interventions	Details of intervention: • Dose: dexamethasone: 6 mg/day during 10 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): dexamethasone: 20 mg/IV/ daily from day of randomisation (day 1) during 5 days, followed by 10 mg/IV/ daily from day 6-10 of randomisation Concomitant therapy: no information
Outcomes	Primary outcome: all-cause mortality at 60 days after randomisation
Starting date	8 February 2021
Contact information	Jesús Villar, MD+34606860027 NCT04545242, ICI20-00062, Efficacy of DEXamethasone in Patients With Acute Hypoxemic REspiratory Failure Caused by INfEctions" type="EXTERNAL">jesus.villar54@gmail.com
Notes	Recruitment status: not yet recruiting Prospective completion date: 30 December 2023 Date last update was posted: 22 January 2021 Sponsor/funding: Dr. Negrin University Hospital

NCT04636671

Study name	Methylprednisolone vs. dexamethasone in COVID-19 pneumonia (MEDEAS RCT) (MEDEAS)
Methods	Trial design: open-label RCT Sample size: 680 Setting: inpatient Language: Italian, English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria

NCT04636671 *(Continued)*

- Able to understand and sign the informed consent
- SARS-CoV-2 positive on at least 1 upper respiratory swab or bronchoalveolar lavage
- PaO2 ≤ 60 mmHg or SpO2 ≤ 90% or on HFNC, CPAP or NPPV at randomisation
- Age ≥ 18 years old at randomisation

Exclusion criteria

- On IMV (either intubated or tracheostomised)
- Heart failure as the main cause of acute respiratory failure
- On long-term oxygen or home mechanical ventilation
- Decompensated liver cirrhosis
- Immunosuppression (i.e. cancer on treatment, post-organ transplantation, HIV-positive, on immunosuppressant therapy)
- Chronic renal failure with dialysis dependence
- Progressive neuro-muscular disorders
- Cognitively impaired, dementia or decompensated psychiatric disorder
- Quadriplegia/hemiplegia or quadriparesis/hemiparesis
- Do-not-resuscitate order
- Previous or current use of remdesivir
- Participating in other clinical trial including experimental compound with proved or expected activity against SARS-CoV-2 infection
- Any other condition that in the opinion of the investigator may significantly impact with patient's capability to comply with protocol intervention

Interventions	Details of intervention
	• Dose:
	  ○ A. On day 1, loading dose of methylprednisolone 80 mg IV in 30 min, promptly followed by continuous infusion of methylprednisolone 80 mg/d in 240 mL of normal saline at 10 mL/h.
	  ○ B. From day 2-8: infusion of methylprednisolone 80 mg/day in 240 mL of normal saline at 10 mL/h. C. From day 9 and beyond: if not intubated patient and PaO2/FiO2 > 200, taper to methylprednisolone 20 mg IV in 30 min 3 times a day for 3 days, then methylprednisolone 20 mg IV twice daily for 3 days, then methylprednisolone 20 mg IV once daily for 2 days, then switch to methylprednisolone 16 mg/day orally for 2 days, then methylprednisolone 8 mg/day orally for 2 days, then methylprednisolone 4 mg/day orally for 2 days; if intubated patient or PaO2/FiO2 ≤ 200 with at least 5 cmH2O CPAP, continue infusion of methylprednisolone 80 mg/day in 240 mL of normal saline at 10 mL/h until PaO2/FiO2 > 200 then taper as in a)
	• Route of administration: IV
	Treatment details of control group (e.g dose, route of administration): A. dexamethasone 6 mg IV in 30 min or orally from day 1-10 or until hospital discharge (if sooner). B. After day 10 study treatment is interrupted.
	Concomitant therapy: no information

Outcomes	Primary outcome: survival proportion at 28 days in both arms
Starting date	25 November 2020
Contact information	Marco Confalonieri, MD+390403994667 NCT04636671, MEDEAS1, Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia (MEDEAS RCT)" type="EXTERNAL">mconfalonieri@units.it
Notes	Recruitment status: recruiting Prospective completion date: estimated primary completion date 31 March 2021; estimated study completion date 30 April 2021 Date last update was posted: 19 November 2020

NCT04636671 *(Continued)*	Sponsor/funding: University of Trieste and Centro di Riferimento Oncologico - Aviano and National Institute for the Infectious Diseases (L. Spallanzani) - Rome

NCT04663555	
Study name	Effect of two different doses of dexamethasone in patients with ARDS and COVID-19 (REMED)
Methods	Trial design: prospective, phase II, open-label, RCT Sample size: 300 Setting: inpatient Language: Czech, English Number of centres: 11 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Adult (≥ 18 years of age) at time of enrolment • Present COVID-19 (infection confirmed by RT-PCR or antigen testing) • Intubation/mechanical ventilation or ongoing HFNC oxygen therapy • Moderate or severe ARDS according to Berlin criteria: moderate - PaO2/FiO2 100-200 mmHg; severe - PaO2/FiO2 < 100 mmHg • Admission to ICU in the last 24 h Exclusion criteria • Known allergy/hypersensitivity to dexamethasone or excipients of the investigational medicinal product (e.g. parabens, benzyl alcohol) • Fulfilled criteria for ARDS for ≥ 14 days at enrolment • Pregnancy or breastfeeding • Unwillingness to comply with contraception measurements from enrolment to at least 1 week after the last dose of dexamethasone (sexual abstinence is considered as adequate contraception method) • End-of-life decision or patient is expected to die within next 24 h • Decision not to intubate or ceilings of treatment in place • Immunosuppression and/or immunosuppressive drugs in medical history: • Systemic immunosuppressive drugs or chemotherapy in the past 30 days • Systemic corticosteroid use before hospitalisation • Any dose of dexamethasone during the present hospital stay for COVID-19 for ≥ last 5 days before enrolment • Systemic corticosteroids during present hospital stay for other conditions than COVID-19 (e.g. septic shock) • Present haematological or generalised solid malignancy • Any of contraindications of corticosteroids, e.g. intractable hyperglycaemia; active gastrointestinal bleeding; adrenal gland disorders; a presence of superinfection diagnosed with locally established clinical and laboratory criteria without adequate antimicrobial treatment • Cardiac arrest before ICU admission • Participation in another interventional trial in the last 30 days
Interventions	Details of intervention

NCT04663555 *(Continued)*

	• Dose: dexamethasone 20 mg once daily on day 1-5, followed by dexamethasone 10 mg IV once daily on day 6-10 • Route of administration: IV Treatment details of control group (e.g dose, route of administration): dexamethasone 6 mg day 1-10 Concomitant therapy: no information
Outcomes	Primary outcome: number of ventilator-free days at 28 days after randomisation, defined as being alive and free from mechanical ventilation (> 48 h)
Starting date	
Contact information	Jan Maláska, MD, PhD, EDIC+420723784101 NCT04663555, CZECRIN No. 2020/47, Effect of Two Different Doses of Dexamethasone in Patients With ARDS and COVID-19" type="EXTERNAL">jan.malaska@gmail.com
Notes	Recruitment status: recruiting Prospective completion date: 31 March 2021 Date last update was posted: 4 February 2021 Sponsor/funding: Brno University Hospital

NCT04673162

Study name	Evaluation of the efficacy of high doses of methylprednisolone in SARS-CoV2 (COVID-19) pneumonia patients
Methods	Trial design: quadruple-blind, multicentric, randomised study Sample size: 260 Setting: inpatient Language: Italian, English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age = 18 years • Informed consent for participation in the study and for data processing • Molecular diagnosis with PCR test of Sars-CoV2 infection • Hospitalisation in a specialist ward for COVID-19 patient care (e.g. Infectious Diseases, Pulmonology or Internal Medicine) • Need for supplemental oxygen in any delivery mode with the exception of IMV • PaO2 / FiO2 between 100 and 300 mmHg • Clinical/instrumental diagnosis (high-resolution chest CT scan or chest X-ray or lung ultrasound) of interstitial pneumonia for no more than 3 days • Serum CRP > 5 mg / dL • Interval from onset of SARS-CoV2 infection symptoms to randomisation > 5 days Exclusion criteria

NCT04673162 *(Continued)*

	• IMV • Presence of shock or concomitant organ failure that requires admission to the ICU • Pregnancy or breastfeeding • Severe heart or kidney failure • Known hypersensitivity to methylprednisolone, to dexamethasone or to an exception • Diabetes not compensated according to the doctor's judgment • Other clinical conditions that contraindicate methylprednisolone and cannot be treated or resolved according to the doctor's judgment • Steroid bolus therapy in the week prior to enrolment for the study • Enrolment in another clinical trial • Patient already randomised in this study
Interventions	Details of intervention • Dose: standard treatment (currently dexamethasone 6 mg/daily for 10 days) plus methylprednisolone 1 g daily on days 1, 2, 3 • Route of administration: IV Treatment details of control group (e.g dose, route of administration): standard treatment (currently dexamethasone 6 mg/daily for 10 days) plus placebo Concomitant therapy: no information
Outcomes	Primary study outcome • Time to recovery (discharge from hospital) • Invasive ventilation prevention • Survival
Starting date	
Contact information	Massimo Costantini, MD+390522296986 NCT04673162, RCT-MP-COVID-19, Evaluation of the Efficacy of High Doses of Methylprednisolone in SARS-CoV2 (COVID-19) Pneumonia Patients" type="EXTERNAL">massimo.costantini@ausl.re.it
Notes	Recruitment status: not yet recruiting Prospective completion date: estimated primary completion date April 2021; estimated study completion date June 2021 Date last update was posted: 17 December 2020 Sponsor/funding: Azienda Unità Sanitaria Locale Reggio Emilia

NCT04707534

Study name	Dexamethasone for COVID-19
Methods	Trial design: open-label RCT Sample size: 300 Setting: inpatient Language: English Number of centres: no information

NCT04707534 *(Continued)*

	Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age ≥ 18 years old • RT-PCR confirmed COVID-19 infection • Positive pressure ventilation (non-invasive or invasive) or HFNC or need supplemental oxygen with oxygen mask or nasal cannula Exclusion criteria • Underlying disease requiring chronic corticosteroids • Severe adverse events before admission, i.e. cardiac arrest • Contraindication for corticosteroids • Death is deemed to be imminent and inevitable during the next 24 h • Recruited in other clinical intervention trial • Pregnancy • Patient on judicial protection
Interventions	Details of intervention • Dose: dexamethasone 20 mg daily for 5 days, followed by dexamethasone 10 mg daily for 5 days • Route of administration: no information Treatment details of control group (e.g dose, route of administration): dexamethasone 6 mg daily for 10 days Concomitant therapy: no information
Outcomes	Primary outcome: 8-scale World Health Organisation ordinal scale at day 28
Starting date	21 January 2021
Contact information	Huimin Wu, MD MPH(405) 271-6173 NCT04707534, 12927, Dexamethasone for COVID-19" type="EXTERNAL">Huimin-Wu@ouhsc.edu
Notes	Recruitment status: recruiting Prospective completion date: 21 June 2021 Date last update was posted: 8 January 2021 Sponsor/funding: University of Oklahoma

NCT04726098

Study name	Low or high dose of dexamethasone in patients with respiratory failure by COVID-19 (HIGHLOWDEXA)
Methods	Trial design: open-label RCT Sample size: 198 Setting: inpatient Language: Spanish, English Number of centres: no information

NCT04726098 *(Continued)*

	Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Age ≥ 18 years • Hospitalised COVID-19 patients admitted to the Hospital • Patients requiring supplemental oxygen • Level 4 using the WHO 7-point Ordinal Scale for clinical improvement • Patients requiring corticosteroids (dexamethasone) according to hospital protocol Exclusion criteria • Pregnancy or active lactation • Patient is expected to die in the next 48 h • Known history of dexamethasone allergy or known contraindication to the use of corticosteroids • Daily use of corticosteroids in the past 15 days • Indication for corticosteroids use for other clinical conditions (e.g. refractory septic shock) • Consent refusal for participating in the trial • Different level from 4 using the WHO 7-point Ordinal Scale for clinical improvement
Interventions	Details of intervention • Dose: dexamethasone 6 mg/day for 10 days • Route of administration: most likely systemic Treatment details of control group (e.g dose, route of administration): dexamethasone 20 mg/day for 5 days + dexamethasone 10 mg/day for 5 days (total 10 days) Concomitant therapy: no information
Outcomes	Primary outcome: percentage of patients with treatment failure at day 11 defined as death, need of ICU and ECMO, need of NIV or nasal high-flow oxygen therapy, or worsening of the clinical condition of the patient during treatment (2 of these: need to increase: fraction of inspired oxygen inspired > 20%, need for fraction inspired oxygenation > 50%, increase in respiratory rate > 25, increase in inflammatory markers)
Starting date	15 January 2021
Contact information	Manuel Taboada Muñiz, Ph.D.+34678195618 NCT04726098, HIGHLOWDEXA-COVID, Low or High Dose of Dexamethasone in Patients With Respiratory Failure by COVID-19" type="EXTERNAL">manutabo@yahoo.es
Notes	Recruitment status: recruiting Prospective completion date: estimated primary completion date 30 June 2021; estimated study completion date 31 December 2022 Date last update was posted: 27 January 2021 Sponsor/funding: Manuel Taboada Muñiz

NCT04765371

Study name	Comparison between prednisolone and dexamethasone on mortality in patients on oxygen therapy, with COVID-19 (COPreDex)
Methods	Trial design: open-label RCT

NCT04765371 *(Continued)*

	Sample size: 220 Setting: inpatients Language: French, English Number of centres: 6 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Patient ≥ 18 years old • Patient with SARS-CoV-2 pneumopathy documented by nasopharyngeal or bronchoalveolar lavage fluid RT-PCR or any documented clinical symptoms support by CT scan • Patient with SpaO2 ≤ 94 % in room air (90% for patient with respiratory failure) and requiring an oxygen therapy • Negative pregnancy test for women of childbearing age • Informed and written informed consent (IC) obtained • Patients with affiliation to the social security system Exclusion criteria • Patient with corticosteroids as background treatment (≥ 10 mg equivalent) • Patient under supplemental oxygen > 6 L/min • Immunocompromised patient (AIDS, bone marrow or solid organ transplants, etc.) • Patient who received a corticosteroid dose within 3 days for COVID-19 • Medical history of hypersensitivity to prednisolone or dexamethasone; or lactose/galactose (excipients with known effect) • Another active virus such hepatitis, herpes, varicella, shingles, etc. • Psychotic state not controlled by treatment
Interventions	Details of intervention • Dose: 6 mg/d of dexamethasone during 10 days • Route of administration: most likely systemic Treatment details of control group (e.g dose, route of administration): 60 mg/d of prednisolone during 10 days Concomitant therapy: no information
Outcomes	Primary outcome: mortality assessment at day 28
Starting date	March 2021
Contact information	Maryline Delattre 0033130754131 NCT04765371, CHRD1520, Comparison Between Prednisolone and Dexamethasone on Mortality in Patients on Oxygen Therapy, With CoViD-19" type="EXTERNAL">maryline.delattre@ght-novo.fr
Notes	Recruitment status: recruiting Prospective completion date: October 2021 Date last update was posted: 1 March 2021 Sponsor/funding: Centre Hospitalier René Dubos

NCT04780581

Study name	Glucocorticoid therapy in coronavirus disease COVID-19 patients
Methods	Trial design: open-label RCT Sample size: 290 Setting: inpatient Language: Spanish, English Number of centres: 5 Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • > 18 years of age • Inpatient • Diagnosis of SARS-CoV-2 infection confirmed by RT-PCR or antigen • Present evidence in CT of pulmonary involvement attributed to the infection by COVID • Patients in whom CT scans are not performed must have suspected pulmonary involvement by clinical examination with simple compatible or suggestive radiology • Requires supplementary oxygen due to basal saturation ≤ 93% (with ambient O2, 21%) Exclusion criteria • Patient's situation is so serious that the doctor in charge thinks he could die within 24 • At the time of randomisation, patients require one of the following 4 ventilatory supports: high-flow oxygen devices, mechanical NIV, IMV, ECMO. • The patient is or has been treated in the 2 weeks prior to randomisation with glucocorticoids or inflammation-modifying drugs, both conventional (thiopurines, cyclophosphamide, cyclosporine, tacrolimus), leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, hydroxychloroquine or chloroquine) as synthetics or biologics directed against therapeutic targets (abatacept, belimumab, CD-20, IL1, IL6, Il12. 23, IL-23, Il.17, TNF, integrin α4β7 or Janus kinase inhibitors JAK). Patients who are only on maintenance treatment with doses of steroids less than or equal to 7.5 mg of prednisone or equivalent per day will not be excluded. • The patient is pregnant or breastfeeding. • The patient has a chronic renal disease in stage 4 or 5 (CCr <30 ml/min) • Moderate to severe dementia at the investigator's discretion • Hypersensitivity to any of the active ingredients or to any of the excipients included in its formulation • Untreated systemic infections not caused by COVID-19 • Active stomach or duodenal ulcer • Recent vaccination with live vaccines • Other infection or disease that explains the lung disorder • Inability of the patient to understand the study or to sign the informed consent unless consent is delegated to a legal representative • Active participation in another clinical study in the last 15 days.
Interventions	Details of intervention • Dose: intermediate-dose dexamethasone (6 mg/24 h - 10 days) • Route of administration: most likely systemic Treatment details of control group (e.g dose, route of administration): high-dose methylprednisolone bolus (250 mg/4 h - 3 days) Concomitant therapy: no information

NCT04780581 *(Continued)*

Outcomes	Primary outcome: mortality rate in COVID-19 patients after high-dose methylprednisolone bolus administration versus mortality rate intermediate-dose dexamethasone pattern (time frame: 28 days)
Starting date	1 February 2021
Contact information	Luis Corral Gudino983 420400 NCT04780581, MP3-pulses-COVID-19, Glucocorticoid Therapy in Coronavirus Disease COVID-19 Patients" type="EXTERNAL">lcorral@saludcastillayleon.es
Notes	Recruitment status: recruiting Prospective completion date: 31 December 2021 Date last update was posted: 3 March 2021 Sponsor/funding: Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León

NCT04795583

Study name	Corticosteroids for COVID-19 (CORE-COVID)
Methods	Trial design: interventional, randomised, placebo-controlled, triple-blinded, adaptive clinical trial Sample size: 1526 Setting: outpatient Language: English Number of centres: no information Type of intervention (treatment/prevention): treatment

Participants	Inclusion criteria
	• Age ≥ 18 years
	• Microbiologically-confirmed SARS-CoV-2
	• Clinical symptoms compatible with COVID-19 for ≤ 14 days before randomisation
	• Oxygen saturation ≥ 95%
	• Protein C-reactive in blood performed by point-of-care testing ≥ 20 mg/L
	• Signed informed consent
	Exclusion criteria
	• Oxygen requirement at home due to chronic lung disease
	• Patients with immunosuppression or immunosuppressive therapies defined as:
	  ○ Cancer on active chemotherapy.
	  ■ Stem cell transplant in the previous 6 months.
	  ■ Neutrophil count < 1000 cells/mm3.
	  ■ Chronic treatment with immunosuppressive therapy, except for low-dose (≤ 10 mg daily) prednisone or equivalent dose of other corticosteroids.
	• HIV-infected patients with CD4 < 200 x 106/L
	• Diagnosis with primary immunodeficiencies.
	• Chronic liver damage Child-Pugh C.
	• Chronic underlying process with suspected life expectancy < 12 weeks.
	• Uncontrolled diabetes mellitus at screening, defined as no blood glucose testing or any blood glucose level > 14 mmol/L (or 250 mg/dL) in the last 14 days

NCT04795583 *(Continued)*

	• Diagnosis of any form of psychosis without receiving appropriate treatment • Pregnancy at time of randomisation • Patients who received approved or trial vaccination for SARS-CoV-2

Interventions	Details of intervention:
	• Dose: prednisone 25 mg capsules
	  ○ ≤ 50 kg = 2 capsules every day for 7 days (maximum dose = 50 mg/day)
	  ○ 50-80kg = 3 capsules every day for 7 days (maximum dose = 75 mg/d)
	  ○ > 80 kg = 4 capsules every day for 7 days (maximum dose = 100 mg/d)
	• Route of administration: oral
	Treatment details of control group (e.g dose, route of administration): capsules with the same appearance as prednisone
	Concomitant therapy: no information

Outcomes	Primary outcome • Need to be admitted to hospital or • Death during the first 2 weeks after randomisation
Starting date	April 2021
Contact information	Carlos Cervera, MD, PhD780-492-5346 NCT04795583, 00001, Corticosteroids for COVID-19" type="EXTERNAL">cerveraa@ualberta.ca
Notes	Recruitment status: not yet recruiting Prospective completion date: August 2022 Date last update was posted: 18 March 2021 Sponsor/funding: University of Alberta

NCT04834375

Study name	Randomised open investigation determining steroid dose (ROIDS-Dose)
Methods	Trial design: randomised, open-label trial Sample size: 142 Setting: probably inpatient Language: English Number of centres: single centre Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Adults ≥ 18 years old • COVID-19 infection confirmed by positive PCR test • Hypoxaemia defined by an oxygen saturation < 94% or the need for supplemental oxygen Exclusion criteria

NCT04834375 *(Continued)*

	• Corticosteroid use for > 48 h within the past 15 days prior to enrolment • Use of steroids with doses > the equivalent to dexamethasone 6 mg • Use of immunosuppressive drugs • Pregnant women • Chronic oxygen use • Known history of dexamethasone allergy • Do-not-resuscitate/do-not-intubate orders • Patient or proxy cannot consent
Interventions	Details of intervention • Dose: dexamethasone 6 mg daily for 10 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): dexamethasone 0.2 mg/kg/d IV (maximum 20 mg daily) for 10 days Concomitant therapy: no information
Outcomes	Primary outcome: all-cause mortality at 28 days
Starting date	19 March 2021
Contact information	Carlos X Rabascall, MD5164655400 NCT04834375, 21-0171, Randomized Open Investigation Determining Steroid Dose" type="EXTERNAL">crabascallay@northwell.edu
Notes	Recruitment status: recruiting Prospective completion date: 19 April 2022 Date last update was posted: 8 April 2021 Sponsor/funding: Northwell Health

NCT04836780

Study name	Dexamethasone early administration in hospitalised patients with COVID-19 pneumonia (EARLY-DEXCoV2)
Methods	Trial design: prospective, multicenter, phase-4, parallel-group, open-label RCT Sample size: 126 Setting: inpatient Language: Spanish, English Number of centres: no information Type of intervention (treatment/prevention): treatment
Participants	Inclusion criteria • Adults (age ≥ 18 years) • Diagnosed with SARS-CoV-2 infection by PCR or rapid antigen test on upper respiratory tract (nasopharyngeal and oropharyngeal) specimens. • Evidence of infiltrates on chest radiography or CT

NCT04836780 *(Continued)*

	• Peripheral capillary oxygen saturation (SpO2) ≥ 94% and < 22 breaths per min (bpm) breathing room air • High risk of developing ARDS defined by a LDH > 245 U/L, C-RP > 100 mg/L, and absolute lymphocytes < 800 cells/µL • Eligible participants will meet 2/3 above analytical criteria associated with severe COVID-19 • Patients will provide written informed consent or who have a legally authorised representative available to do so. In these exceptional circumstances and following the recommendations of the Spanish Agency of Medicines and Medical Devices, the National Competent Authority of clinical trials, during the coronavirus crisis to avoid the risk of contagion, consent will be possible to obtained orally in the presence of at least one impartial witness. Exclusion criteria • Patients with a history of allergy to dexamethasone • Pregnant or lactating women • Oral or inhaled corticosteroids treatment within 15 days before randomisation • Immunosuppressive agent or cytotoxic drug therapy within 30 days before randomisation • Neutropenia < 1000 cells/µL • HIV infection with CD4 cell counts < 500 cells within 90 days after randomisation • Dementia • Chronic liver disease defined by ALT or AST ≥ 5 times the ULN. • Chronic kidney injury defined by a glomerular filtration rate ≤ 30 mL/min, haemodialysis or peritoneal dialysis • Uncontrolled infection • Patients who are already enrolled in another clinical trial
Interventions	Details of intervention: • Dose: dexamethasone base 6 mg once daily for 7 days • Route of administration: IV Treatment details of control group (e.g dose, route of administration): standard care therapy Concomitant therapy: no information
Outcomes	Primary outcome • The primary trial outcome is the development of moderate-severe ARDS (time frame: 7 days), based on the Berlin criteria. • The collected data as outcome measure will be general vital signs, Sequential Organ Failure Assessment (SOFA) score, the clinical status of the patient using the ordinal scale of the WHO, SpO2, PaO2/FiO2 ratio calculated from SpO2/FiO2, blood routine tests and chest radiography. • Concomitant drugs and adverse event monitoring will be collected. • Data will be measured during admission. • Participants will schedule for a follow-up visit on the 30th and 90th day to track their long-term prognosis, clinical status and sequelae
Starting date	Nno information
Contact information	Anabel Franco Moreno, MD, PhD +34 911 91 80 00 NCT04836780, EARLY-DEX Covid-19, DEXamethasone EARLY Administration in Hospitalized Patients With Covid-19 Pneumonia" type="EXTERNAL">afranco278@hotmail.com
Notes	Recruitment status: not yet recruiting Prospective completion date: 30 June 2021 Date last update was posted: 8 April 2021

NCT04836780 *(Continued)*

Sponsor/funding: Hospital Universitario Infanta Leonor

AHRF: acute hypercapnic respiratory failure; **ALT:** alanine transaminase; **APPT:** activated partial thromboplastin time; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate transaminase; **CT:** computed tomography; **ECG:** echocardiogram; **ECMO:** extracorporeal membrane oxygenation; **FiO2:** fraction of inspired oxygen; **HFNC:** high-flow nasal cannula; **HFNO:** high-flow nasal oxygen; **ICU: i**ntensive care unit; **IMV:** invasive mechanical ventilation; **IV:** intravenous; **LMWH:** low molecular weight heparin; **NLR:** neutrophil-lymphocyte ratio; **NPPV:** non-invase positive pressure ventilation; PCR: polymerase chain reaction; **PEEP:** positive end-expiratory pressure; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SC:** subcutaneously; **SpO2:** blood oxygen saturation; **ULN:** upper limit of normal

RISK OF BIAS

Legend: Low risk of bias; High risk of bias; Some concerns

Risk of bias for analysis 1.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Angus 2020	+	~	+	+	+	~
Angus 2020	+	~	+	+	+	~
Corral-Gudino 2021	~	+	+	+	~	~
Dequin 2020	+	+	+	+	~	~
Edalatifard 2020	~	~	+	+	~	~
Horby 2021	+	~	+	+	+	~
Jamaati 2021	~	+	+	+	~	~
Jeronimo 2020	+	~	+	+	+	~
Tang 2021	+	+	+	+	+	+
Tomazini 2020	+	~	+	+	+	~

Risk of bias for analysis 1.2 Clinical improvement: Liberation from IMV

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jeronimo 2020	✓	~	✗	✓	~	✗
Tomazini 2020	✓	~	✗	✓	✓	✗

Risk of bias for analysis 1.3 Clinical improvement: Ventilator-free days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Tomazini 2020	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.4 Clinical worsening: New need for IMV

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Corral-Gudino 2021	~	✓	✗	✓	~	✗
Edalatifard 2020	~	~	✗	✓	~	✗
Jamaati 2021	~	✓	✗	✓	~	✗
Jeronimo 2020	✓	~	✗	✓	~	✗

Risk of bias for analysis 1.5 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Angus 2020	✓	~	✗	✓	✓	~
Angus 2020	✓	~	✗	✓	✓	~
Tomazini 2020	✓	~	✗	✓	✓	✗

Risk of bias for analysis 1.6 Adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Corral-Gudino 2021	~	✓	✗	✓	~	✗
Dequin 2020	✓	✓	✗	✓	✓	✗
Edalatifard 2020	~	~	✗	✓	~	✗
Tang 2021	✓	✓	✗	✓	~	✗
Tomazini 2020	✓	~	✗	✓	✓	✗

Risk of bias for analysis 1.7 Hospital-acquired infections

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Corral-Gudino 2021	~	✓	✗	✓	~	✗
Dequin 2020	✓	✓	✗	✓	✓	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Edalatifard 2020	~	~	✗	✓	~	✗
Tang 2021	✓	✓	✗	✓	~	✗
Tomazini 2020	✓	~	✗	✓	✓	✗

Risk of bias for analysis 1.8 Need for dialysis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Horby 2021	✓	~	✗	✓	✓	✗
Jeronimo 2020	✓	~	✗	✓	✓	✗

Risk of bias for analysis 1.9 Viral clearance

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jeronimo 2020	✓	~	✗	✓	✓	✗

Risk of bias for analysis 2.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 Invasive ventilation						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Horby 2021	✓	~	✓	✓	✓	~
Jeronimo 2020	✓	~	✓	✓	✓	~
Tomazini 2020	✓	~	✓	✓	✓	~
Subgroup 2.1.2 NIV or high-flow oxygen only						
Corral-Gudino 2021	~	✓	✓	✓	~	~
Edalatifard 2020	~	~	✓	✓	~	~
Jeronimo 2020	✓	~	✓	✓	✓	~
Subgroup 2.1.3 NIV, high-flow, and low-flow oxygen combined						
Horby 2021	✓	~	✓	✓	✓	~
Subgroup 2.1.4 Low-flow-oxygen only						
Corral-Gudino 2021	~	✓	✓	✓	~	~
Edalatifard 2020	~	~	✓	✓	~	~
Jeronimo 2020	✓	~	✓	✓	✓	~
Subgroup 2.1.5 No oxygen						
Horby 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 3.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.1.1 Dexamethasone						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Horby 2021	✓	~	✓	✓	✓	~
Jamaati 2021	~	✓	✓	✓	~	~
Tomazini 2020	✓	~	✓	✓	✓	~
Subgroup 3.1.2 Methylprednisolone						
Corral-Gudino 2021	~	✓	✓	✓	~	~
Edalatifard 2020	~	~	✓	✓	~	~
Jeronimo 2020	✓	~	✓	✓	✓	~
Tang 2021	✓	✓	✓	✓	✓	✓
Subgroup 3.1.3 Hydrocortisone						
Angus 2020	✓	~	✓	✓	✓	~
Angus 2020	✓	~	✓	✓	✓	~
Dequin 2020	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ranjbar 2021	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.2 Clinical worsening: New need for IMV

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ranjbar 2021						

DATA AND ANALYSES

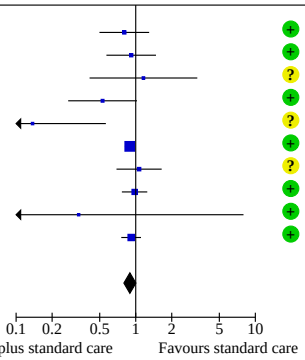
Comparison 1. Systemic corticosteroids plus standard care versus standard care (plus/minus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	9	7930	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 1.00]
1.2 Clinical improvement: Liberation from IMV	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3 Clinical improvement: Ventilator-free days	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.4 Clinical worsening: New need for IMV	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.5 Serious adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6 Adverse events	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7 Hospital-acquired infections	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.8 Need for dialysis	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.9 Viral clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 1: All-cause mortality

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Angus 2020 (1)	37	141	17	52	5.3%	0.80 [0.50 , 1.29]	+ ? + + + ?
Angus 2020 (2)	41	137	16	49	5.3%	0.92 [0.57 , 1.48]	+ ? + + + ?
Corral-Gudino 2021	7	35	5	29	1.2%	1.16 [0.41 , 3.27]	? + + + ? ?
Dequin 2020	11	76	20	73	2.9%	0.53 [0.27 , 1.02]	+ + + + ? ?
Edalatifard 2020	2	34	12	28	0.7%	0.14 [0.03 , 0.56]	? ? + + ? ?
Horby 2021	482	2104	1110	4321	40.4%	0.89 [0.81 , 0.98]	+ ? + + + ?
Jamaati 2021	16	25	15	25	6.2%	1.07 [0.69 , 1.65]	? + + + ? ?
Jeronimo 2020	79	209	80	207	15.9%	0.98 [0.77 , 1.25]	+ ? + + + ?
Tang 2021	0	43	1	43	0.1%	0.33 [0.01 , 7.96]	+ + + + + +
Tomazini 2020	85	151	91	148	22.1%	0.92 [0.76 , 1.11]	+ ? + + + ?
Total (95% CI)		**2955**		**4975**	**100.0%**	**0.89 [0.80 , 1.00]**	
Total events:	760		1367				

Heterogeneity: Tau² = 0.01; Chi² = 11.34, df = 9 (P = 0.25); I² = 21%
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable

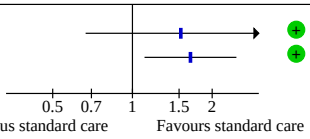


Footnotes
(1) Angus 2020 intervention arm: shock-dependent hydrocortisone
(2) Angus 2020 intervention arm: fixed-dose hydrocortisone

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 1.2. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 2: Clinical improvement: Liberation from IMV

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Jeronimo 2020 (1)	12	66	8	67	1.52 [0.67 , 3.48]	+ ? - + ? -
Tomazini 2020 (2)	49	151	29	148	1.66 [1.11 , 2.47]	+ ? - + + -

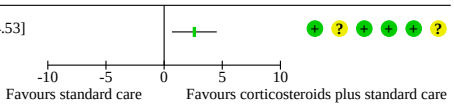


Footnotes
(1) Liberation from invasive ventilation at day 28
(2) Liberation from invasive ventilation at day 15

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Clinical improvement: Liberation from IMV
(C) Bias due to missing outcome data: Clinical improvement: Liberation from IMV
(D) Bias in measurement of the outcome: Clinical improvement: Liberation from IMV
(E) Bias in selection of the reported result: Clinical improvement: Liberation from IMV
(F) Overall bias: Clinical improvement: Liberation from IMV

Analysis 1.3. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 3: Clinical improvement: Ventilator-free days

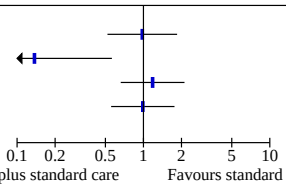
Study or Subgroup	Corticosteroids plus standard care Mean	SD	Total	Standard care Mean	SD	Total	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Tomazini 2020	6.6	9.9504	151	4	6.7715	148	2.60 [0.67 , 4.53]	+ ? + + + ?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Clinical improvement: Ventilator-free days
(C) Bias due to missing outcome data: Clinical improvement: Ventilator-free days
(D) Bias in measurement of the outcome: Clinical improvement: Ventilator-free days
(E) Bias in selection of the reported result: Clinical improvement: Ventilator-free days
(F) Overall bias: Clinical improvement: Ventilator-free days

Analysis 1.4. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 4: Clinical worsening: New need for IMV

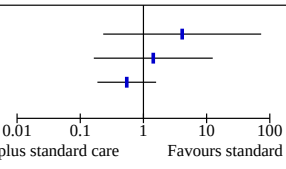
Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Corral-Gudino 2021	13	35	11	29	0.98 [0.52 , 1.85]	? + - + ? -
Edalatifard 2020	2	34	12	28	0.14 [0.03 , 0.56]	? ? - + ? -
Jamaati 2021	13	25	11	25	1.18 [0.66 , 2.11]	? + - + ? -
Jeronimo 2020	19	123	20	128	0.99 [0.56 , 1.76]	+ ? - + ? -



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Clinical worsening: New need for IMV
(C) Bias due to missing outcome data: Clinical worsening: New need for IMV
(D) Bias in measurement of the outcome: Clinical worsening: New need for IMV
(E) Bias in selection of the reported result: Clinical worsening: New need for IMV
(F) Overall bias: Clinical worsening: New need for IMV

Analysis 1.5. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 5: Serious adverse events

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Angus 2020 (1)	5	141	0	52	4.11 [0.23 , 72.98]	+ ? - + + ?
Angus 2020 (2)	4	137	1	49	1.43 [0.16 , 12.49]	+ ? - + + ?
Tomazini 2020	5	151	9	148	0.54 [0.19 , 1.59]	+ ? - + + -

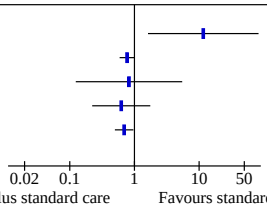


Footnotes
(1) Angus 2020 intervention arm: shock-dependent hydrocortisone
(2) Angus 2020 intervention arm: fixed-dose hydrocortisone

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Analysis 1.6. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 6: Adverse events

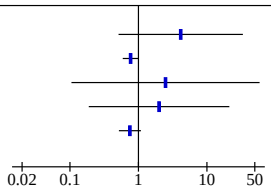
Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Corral-Gudino 2021	14	35	1	29	11.60 [1.62 , 83.03]		?	+	-	+	?	-
Dequin 2020	40	76	50	73	0.77 [0.59 , 1.00]		+	+	-	+	+	-
Edalatifard 2020	2	34	2	28	0.82 [0.12 , 5.48]		?	?	-	+	?	-
Tang 2021	5	43	8	43	0.63 [0.22 , 1.76]		+	+	-	+	?	-
Tomazini 2020	41	151	58	148	0.69 [0.50 , 0.96]		+	?	-	+	+	-



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Adverse events
(C) Bias due to missing outcome data: Adverse events
(D) Bias in measurement of the outcome: Adverse events
(E) Bias in selection of the reported result: Adverse events
(F) Overall bias: Adverse events

Analysis 1.7. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 7: Hospital-acquired infections

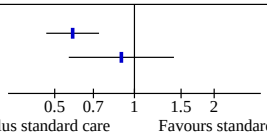
Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Corral-Gudino 2021	5	35	1	29	4.14 [0.51 , 33.49]		?	+	-	+	?	-
Dequin 2020	40	76	50	73	0.77 [0.59 , 1.00]		+	+	-	+	+	-
Edalatifard 2020	1	34	0	28	2.49 [0.11 , 58.74]		?	?	-	+	?	-
Tang 2021	2	43	1	43	2.00 [0.19 , 21.24]		+	+	-	+	?	-
Tomazini 2020	36	151	47	148	0.75 [0.52 , 1.09]		+	?	-	+	+	-



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Hospital-acquired infections
(C) Bias due to missing outcome data: Hospital-acquired infections
(D) Bias in measurement of the outcome: Hospital-acquired infections
(E) Bias in selection of the reported result: Hospital-acquired infections
(F) Overall bias: Hospital-acquired infections

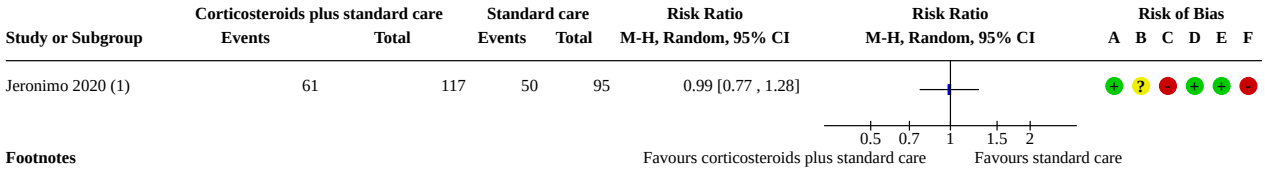
Analysis 1.8. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 8: Need for dialysis

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Horby 2021	89	2034	314	4194	0.58 [0.46 , 0.74]		+	?	-	+	+	-
Jeronimo 2020	29	191	33	194	0.89 [0.57 , 1.41]		+	?	-	+	+	-



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Need for dialysis
(C) Bias due to missing outcome data: Need for dialysis
(D) Bias in measurement of the outcome: Need for dialysis
(E) Bias in selection of the reported result: Need for dialysis
(F) Overall bias: Need for dialysis

Analysis 1.9. Comparison 1: Systemic corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 9: Viral clearance



Footnotes

(1) Jeronimo 2020: Defined as presence of viral RNA in the naso-/oropharyngeal swab at Day 7

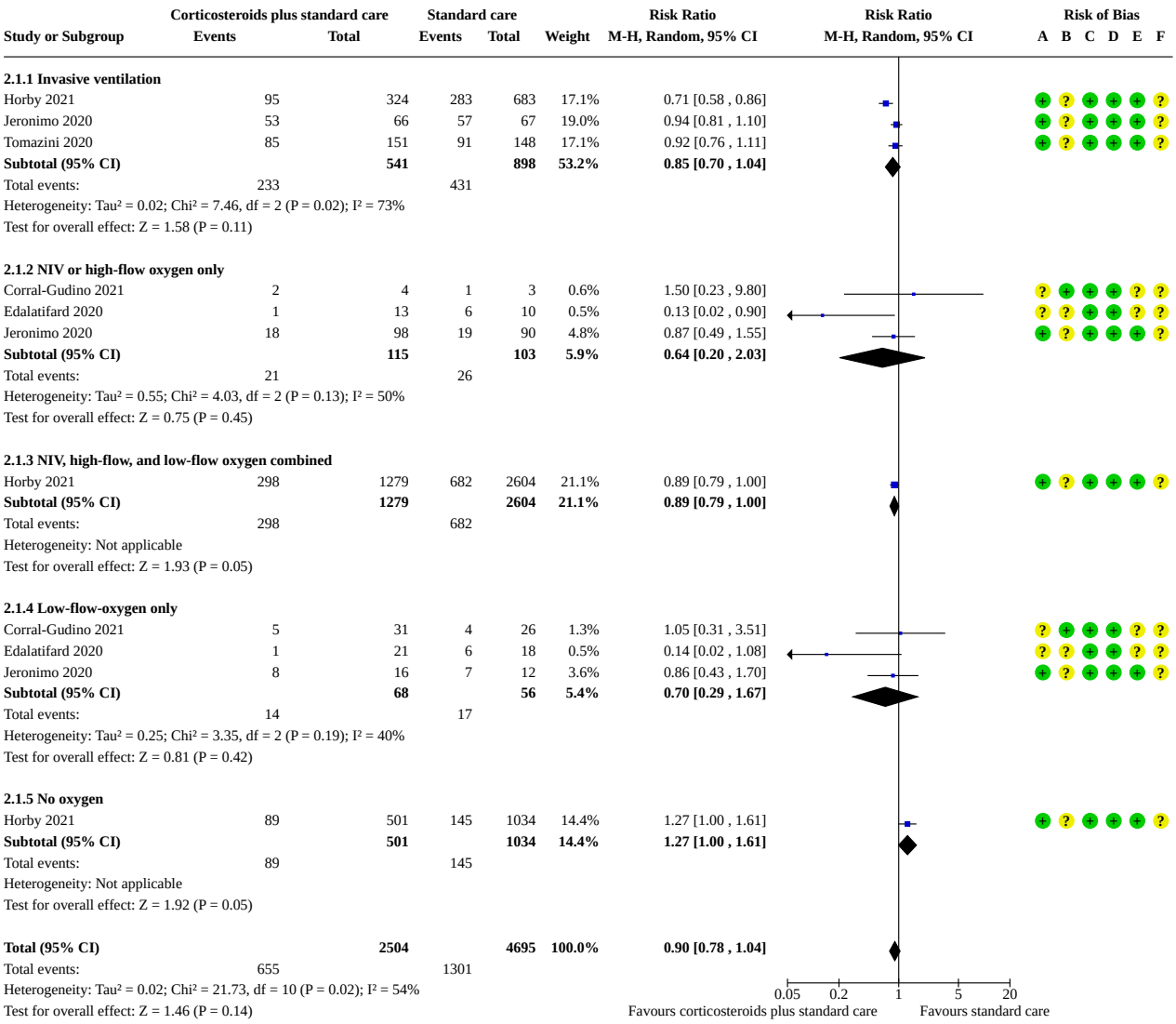
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Viral clearance
(C) Bias due to missing outcome data: Viral clearance
(D) Bias in measurement of the outcome: Viral clearance
(E) Bias in selection of the reported result: Viral clearance
(F) Overall bias: Viral clearance

Comparison 2. Subgroup analysis: respiratory support for the comparison of corticosteroids plus standard care versus standard care (plus/minus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	5	7199	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.04]
2.1.1 Invasive ventilation	3	1439	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.04]
2.1.2 NIV or high-flow oxygen only	3	218	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.20, 2.03]
2.1.3 NIV, high-flow, and low-flow oxygen combined	1	3883	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.00]
2.1.4 Low-flow-oxygen only	3	124	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.29, 1.67]
2.1.5 No oxygen	1	1535	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.00, 1.61]

Analysis 2.1. Comparison 2: Subgroup analysis: respiratory support for the comparison of corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 1: All-cause mortality



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

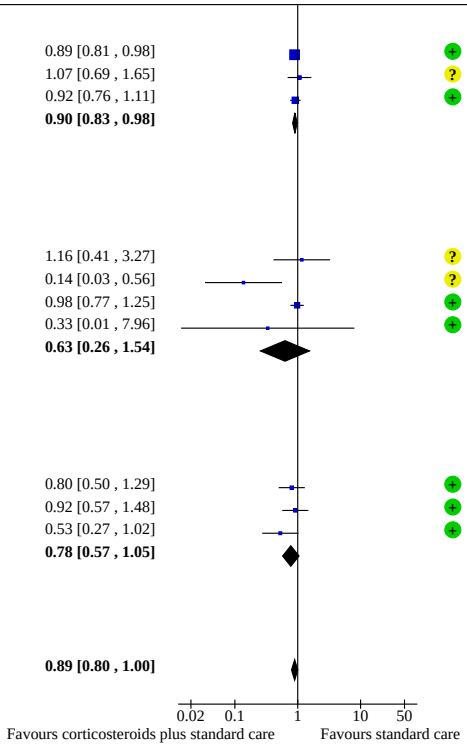
Comparison 3. Subgroup analysis: dexamethasone versus methylprednisolone versus hydrocortisone for the comparison of corticosteroids plus standard care versus standard care (plus/minus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	9	7930	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 1.00]
3.1.1 Dexamethasone	3	6774	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.2 Methylprednisolone	4	628	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.26, 1.54]
3.1.3 Hydrocortisone	2	528	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.57, 1.05]

Analysis 3.1. Comparison 3: Subgroup analysis: dexamethasone versus methylprednisolone versus hydrocortisone for the comparison of corticosteroids plus standard care versus standard care (plus/minus placebo), Outcome 1: All-cause mortality

Study or Subgroup	Corticosteroids plus standard care Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Dexamethasone						
Horby 2021	482	2104	1110	4321	40.4%	0.89 [0.81 , 0.98]
Jamaati 2021	16	25	15	25	6.2%	1.07 [0.69 , 1.65]
Tomazini 2020	85	151	91	148	22.1%	0.92 [0.76 , 1.11]
Subtotal (95% CI)		**2280**		**4494**	**68.7%**	**0.90 [0.83 , 0.98]**
Total events:	583		1216			
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.46 (P = 0.01)						
3.1.2 Methylprednisolone						
Corral-Gudino 2021	7	35	5	29	1.2%	1.16 [0.41 , 3.27]
Edalatifard 2020	2	34	12	28	0.7%	0.14 [0.03 , 0.56]
Jeronimo 2020	79	209	80	207	15.9%	0.98 [0.77 , 1.25]
Tang 2021	0	43	1	43	0.1%	0.33 [0.01 , 7.96]
Subtotal (95% CI)		**321**		**307**	**17.9%**	**0.63 [0.26 , 1.54]**
Total events:	88		98			
Heterogeneity: Tau² = 0.46; Chi² = 8.13, df = 3 (P = 0.04); I² = 63%						
Test for overall effect: Z = 1.02 (P = 0.31)						
3.1.3 Hydrocortisone						
Angus 2020 (1)	37	141	17	52	5.3%	0.80 [0.50 , 1.29]
Angus 2020 (2)	41	137	16	49	5.3%	0.92 [0.57 , 1.48]
Dequin 2020	11	76	20	73	2.9%	0.53 [0.27 , 1.02]
Subtotal (95% CI)		**354**		**174**	**13.4%**	**0.78 [0.57 , 1.05]**
Total events:	89		53			
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Total (95% CI)		**2955**		**4975**	**100.0%**	**0.89 [0.80 , 1.00]**
Total events:	760		1367			
Heterogeneity: Tau² = 0.01; Chi² = 11.34, df = 9 (P = 0.25); I² = 21%						
Test for overall effect: Z = 1.91 (P = 0.06)						
Test for subgroup differences: Chi² = 1.48, df = 2 (P = 0.48), I² = 0%						



Footnotes

(1) Angus 2020 intervention arm: shock-dependent hydrocortisone
(2) Angus 2020 intervention arm: fixed-dose hydrocortisone

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

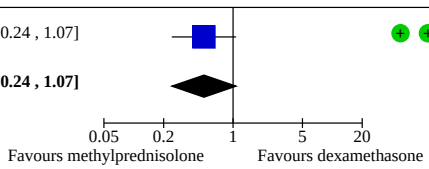
Comparison 4. Methylprednisolone versus dexamethasone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality	1	86	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.24, 1.07]
4.2 Clinical worsening: New need for IMV	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Methylprednisolone versus dexamethasone, Outcome 1: All-cause mortality

Study or Subgroup	Methylprednisolone Events	Total	Dexamethasone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Ranjbar 2021	8	44	15	42	100.0%	0.51 [0.24 , 1.07]	+ + + + ? ?
Total (95% CI)		**44**		**42**	**100.0%**	**0.51 [0.24 , 1.07]**	
Total events:	8		15				

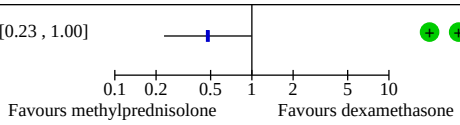
Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 4.2. Comparison 4: Methylprednisolone versus dexamethasone, Outcome 2: Clinical worsening: New need for IMV

Study or Subgroup	Methylprednisolone Events	Total	Dexamethasone Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Ranjbar 2021	8	44	16	42	0.48 [0.23 , 1.00]	+ + - + ? -



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Clinical worsening: New need for IMV
(C) Bias due to missing outcome data: Clinical worsening: New need for IMV
(D) Bias in measurement of the outcome: Clinical worsening: New need for IMV
(E) Bias in selection of the reported result: Clinical worsening: New need for IMV
(F) Overall bias: Clinical worsening: New need for IMV

ADDITIONAL TABLES

Table 1. Characteristics of the included studies for the comparison: corticosteroids versus placebo or standard care

Study ID	Intervention and regimen	Hydrocortisone equivalent of initial dose: for 80 kg bodyweight if applicable (Stoelting 2006)	Control	Randomised to corticosteroids	Randomised to control	Study design	Population/disease severity at randomisation
Angus 2020	Hydrocortisone, IV, 150 mg daily for 7 days	150 mg/d	Standard care	143 (fixed-dose) and 152 (shock-dependent dose)[a]	108	• Platform • Open-label • Multi-centre	Severe ≥ 6
Corral-Gudino 2021	Methylprednisolone, IV 80 mg for 3 days + 40 mg for 3 days	400 mg/d	Standard care	35	29	• Open-label • Multi-centre	Moderate to severe 5-6
Dequin 2020	Hydrocortisone, IV 200 mg for 7 days, 100 mg for 4 days + 50 mg for 3 days	200 mg/d	Placebo	76	73	• Double-blind • Multi-centre	Moderate to severe ≥ 5
Edalatifard 2020	Methylprednisolone, IV, 250 mg for 3 days	1250 mg/d	Standard care	34	34	• Multi-centre	Moderate to severe 5-6
Farahani 2021	Methylprednisolone, IV 1000 mg/d for 3 days + tapering with 1 mg/kg prednisolone for 10 days	5000 mg/d	Standard care	14	15	• Open-label • Single-centre	Moderate to severe 5-6
Horby 2021	Dexamethasone, IV or oral 6 mg daily for 10 days	150 mg/d	Standard care	2104	4321	• Platform • Open-label • Multi-centre	Moderate to severe 4-9
Jamaati 2021	Dexamethasone, IV, 20 mg for 5 days + 10 mg for 5 days	500 mg/d	Standard care	25	25	• Open-label • Single-centre	Most likely moderate 5; no IMV at randomisation
Jeronimo 2020	Methylprednisolone (as sodium succinate), IV 1 mg/kg for 5 days	400 mg/d	Placebo	209	207	• Double-blind • Single-centre	Moderate to severe 5-9
Tang 2021	Methylprednisolone, IV, 1 mg/kg for 7 days	400 mg/d	Placebo	43	43	• Single-blind	Moderate 4-5

Table 1. Characteristics of the included studies for the comparison: corticosteroids versus placebo or standard care *(Continued)*

						• Multi-centre	
Tomazini 2020	Dexamethasone, IV, 20 mg for 5 days + 10 mg for 5 days	500 mg/d	Standard care	151	148	• Open-label • Multi-centre	Severe 7-9

d: day;**IMV:** invasive mechanical ventilation; **IV:** intravenous

[a] Shock-dependent dose: shock-dependent dosing strategy was that restricting hydrocortisone to the period when the patient had overt shock would maximise the risk-benefit ratio. Shock was defined as the requirement for intravenous vasopressor infusion for the treatment of shock presumed due to COVID-19. Hydrocortisone was discontinued in the shock-dependent group once shock was considered to have resolved or vasopressors had been discontinued for 24 hours.

Table 2. Characteristics of the included studies for the comparison: methylprednisolone versus dexamethasone

Study ID	Intervention A	Prednisolone equivalent of initial dose (for 80 kg bodyweight if applicable)	Intervention B	Randomised to intervention A	Randomised to Intervention B	Study design	Population/disease severity at randomisation
Ranjbar 2021	Methylprednisolone, IV 160 mg for 5 days + 80 mg for 5 days + 40 mg for 5 days + 20 mg for 5 days (approximation of tapering scheme)	200 mg/d for methylprednisolone 40 mg/d for dexamethasone	Dexamethasone, IV, 6 mg for 10 days	44	42	• Triple-blind • Single-centre	Moderate 4-5

IV: intravenous

Table 3. Reporting of adverse events

Study	Definition prespecified	Definition as published	Way of counting	Study design
Angus 2020	Trial registration: not mentioned Protocol/SAP: any SAE	Any SAE	Both available	Open-label
Corral-Gudino 2021	Trial registration: use of biological anti-inflammatories	Microbiology-proven infection and hyperglycaemia	Events/patients at risk	Open-label
Dequin 2020	Trial registration: secondary infection during their ICU-stay until day 21 after randomisation Protocol/SAP: no definition	Nosocomial infections until day 28 defined by need for antibiotics. No other SAEs/AEs.	Events/patients at risk	Double-blind
Edalatifard 2020	Trial registration: not mentioned Protocol/SAP: not available	All undesirable effects (adverse events)	Events/patients at risk	Single-blind
Farahani 2021	Trial registration: not mentioned Protocol/SAP: not available	Not reported	Not applicable	Double-blind
Horby 2021	Trial registration: thrombotic events Protocol/SAP: suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs)	Suspected drug reactions reported	Not applicable	Open-label
Jamaati 2021	Not part of trial registration, SAP not available	Not reported	Not applicable	Open-label
Jeronimo 2020	Protocol/SAP: AE: any unwanted medical occurrence SAE: 1. Results in death or puts life at risk; 2. Requires hospitalisation of the patient or extension of an existing hospitalisation; 3. Results in persistent or significant disability; 4. Results in birth defect or congenital anomaly; 5. Constitutes an important event from a clinical point of view.	AE/SAE not explicitly reported. Positive blood culture, need for insulin therapy, sepsis reported.	Blood culture as point prevalence on day 7 Need for insulin therapy and sepsis as patients with event any time within 28 days	Double-blind
Ranjbar 2021	Trial registration: not mentioned Protocol/SAP: not available	Not reported	Not applicable	Triple-blind
Tang 2021	Trial registration: not mentioned Protocol/SAP: not available	Hyperglycaemia, ventilator-associated pneumonia, stress ulcer, gastrointestinal haemorrhage	Events/patients at risk	Single-blind
Tomazini 2020	Trial registration: not mentioned	Glycemic control, nosocomial infection, other AEs	Both available	Open-label

Table 3. Reporting of adverse events *(Continued)*

	Protocol/SAP: glycemic control until day 14, nosocomial infection until day 28, any spontaneous AEs

AE: adverse event; **ICU:** intensive care unit; **SAE:** serious adverse event; **SAP:** statistical analysis plan

Table 4. Characteristics of ongoing studies

Study	Sponsor/developer	Design	Population/disease severity	Setting	Drug	Route of administration	Number of participants	Status
ChiC-TR2000029386	Chongqing Public Health Medical Center	RCT	Severe	Inpatient	Methylprednisolone	IV	48	Recruiting
ChiC-TR2000029656	Wuhan Pulmonary Hospital	RCT	Severe	Inpatient	Methylprednisolone	IV	100	Not yet recruiting
ChiC-TR2000030481	Zhongnan Hospital of Wuhan University	RCT	Diagnosed COVID-19 infection	Inpatient	Early corticosteroid intervention, middle-late corticosteroid intervention	Unclear, most likely systemic	200	Recruiting
CTRI/2020/07/026608	Dr Ananthakumar PK, Chettinad Hospital and Research Institute Kelambakkam Kancheepuram Dist Pin 603103	RCT	Diagnosed COVID-infection + ARDS	Inpatient	Dexamethasone, methylprednisolone	IV	40	Not yet recruiting
CTRI/2020/10/028731	Professor Anders Perner, Senior Staff specialist and professor in Intensive Care Medicine Dept of Intensive Care, Rigshospitalet	RCT	IMV or NIV or continuous use of CPAP for hypoxia or oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system	Inpatient	Dexamethasone	IV	1500	Recruiting
CTRI/2020/12/029944	SRM Medical College Hospital and Research Centre	RCT	SpO_2 < 94% under room air and requiring supplemental oxygen for hypoxemia, respiratory rate 24-30/min	Inpatient	Dexamethasone, methylprednisolone	IV	50	Not yet recruiting
CTRI/2020/12/031443	Maulana Azad Medical College and associated Lok Nayak Hospital	RCT	Admitted to ICU within 14 days of onset of symptoms; receiving invasive or non -invasive positive pressure venti-	Inpatient	Dexamethasone, methylprednisolone	IV	500	Not yet recruiting

Table 4. Characteristics of ongoing studies *(Continued)*

			lation or respiratory support through HFNC					
EUC-TR2020-001413-20-ES	Fundació Clínic per a la Recerca Biomèdica	RCT	Non-critical patient with pneumonia in radiological progression and/or patient with progressive respiratory failure in the last 24-48 h	Inpatient	Methylprednisolone	IV	100	Temporarily halted
EUC-TR2020-001457-43-FR	APHP	RCT	Admitted to ICU	Inpatient	Dexamethasone	IV	550	Ongoing
EUC-TR2020-001622-64-ES	Dra Ana Pueyo Bastida	RCT	Clinical diagnosis of pulmonary involvement (respiratory symptoms +/- pathological auscultation +/- O_2 desaturation) + chest X-ray with mild-moderate or normal alterations	Outpatient	Prednisone	Oral	200	Ongoing
EUC-TR2020-001707-16-ES	Iis Biodonostia	RCT	Bilateral pneumonia caused by SARS-CoV-2 without response to the treatment: defined as persistence of fever (above 37.5 ºC without other focus) and respiratory worsening (more dyspnoea, more cough, oxygen therapy at increasing doses, worsening of the degree of respiratory distress according to the PaO_2 / FiO_2 ratio in categories 'mild, moderate or serious') or absence of improvement with respect to the previous state	Inpatient	Methylprednisolone	IV	60	Ongoing
EUC-TR2020-001921-30	Azienda Ospedaliero-Universitaria Policlinico di Modena	RCT	Positive pressure ventilation (either non-invasive or invasive) from > 24 h, IMV from < 96 h, PaO_2/FiO_2 ratio < 150	Inpatient	Methylprednisolone	IV	200	Ongoing
EUC-TR2020-002186-24-ES	Fundació Hospital Universitari Vall	RCT	Air oxygen saturation > 90 and < 94%; PaO_2/FiO_2 > 200 and ≤ 300 mmHg; Sa:FiO_2 (O_2 saturation mea-	Inpatient	Methylprednisolone	IV	100	Ongoing

Table 4. Characteristics of ongoing studies *(Continued)*

	d'Hebron - Institut de Recerca (VHIR)		sured with pulse oximeter / inspired O_2 fraction) ≤ 350					
EUC-TR2020-003363-25-DK	Department of Intensive Care, Rigshospitalet	RCT	Severe, IMV/NIV	Inpatient	Dexamethasone (high dose and low dose)	IV	1000	Ongoing
EUC-TR2020-004323-16	Azienda Ospedaliera Arcispedale Santa Maria Nuova/IRCCS di Reggio Emilia	RCT	Need for supplemental oxygen in any delivery mode with the exception of IMV	Inpatient	Methylprednisolone	IV	260	Ongoing
NCT04329650	Judit Pich Martínez, Fundacion Clinic per a la Recerca Biomédica	RCT	Non-critical patient with pneumonia in radiological progression and/ or patient with progressive respiratory failure in the last 24-48 h	Inpatient	Methylprednisolone	IV	200	Recruiting
NCT04344730	Assistance Publique - Hôpitaux de Paris	RCT	Admitted to ICU	Inpatient	Dexamethasone	IV	Actual enrolment 550	Not recruiting
NCT04345445	University of Malaya	RCT	Excluded: receipt of mechanical ventilation	Inpatient	Methylprednisolone	IV	310	Not yet recruiting
NCT04347980	Centre Chirurgical Marie Lannelongue	RCT	Admitted to ICU	Inpatient	Dexamethasone	IV	122	Recruiting
NCT04377503	Hospital Sao Domingos	RCT	COVID diagnosis confirmed by real time PCR, PaO_2 / FIO_2 < 200, laboratory: high sensitivity CRP > 5 mg/L; LDH > 245 U/L; ferritin > 300; D-dimer > 1500; interleukin-6> 7.0 pg/mL	Inpatient	Methylprednisolone	Oral	40	Not yet recruiting
NCT04395105	Centro de Educación Medica e Investigaciones Clínicas Norberto Quirno	RCT	ARDS, mechanical ventilated	Inpatient	Dexamethasone	IV	284	Recruiting

Table 4. Characteristics of ongoing studies *(Continued)*

NCT04438980	Fundacion Miguel Servet	RCT	Hospitalised; excluded: SpO_2 < 90% (in air ambient) or PaO_2 < 60 mmHg (in ambient air) or PaO_2/FiO_2 < 300 mmHg	Inpatient	Methylprednisolone	IV	72	Recruiting
NCT04451174	University of Chile	RCT	Excluded: requirements of mechanical ventilation (IMV/NIV) Included: oxygen requirements until 35 % by venturi mask or 5 L/min by nasal cannula	Inpatient	Prednisone	IV	184	Recruiting
NCT04452565	NeuroActiva, Inc.	RCT	Excluded: IMV	Inpatient	Dexamethasone	Oral	525	Recruiting
NCT04485429	D'Or Institute for Research and Education	RCT	Excluded: imminence of orotracheal intubation Included: O_2 saturation in ambient air less ≤ 93%	Inpatient	Methylprednisolone	IV	268	Recruiting
NCT04499313	Chattogram General Hospital	RCT	Moderate to severe COVID-19 infection	Inpatient	Dexamethasone, methylprednisolone	IV	60	Recruiting
NCT04509973	Scandinavian Critical Care Trials Group	RCT	IMV OR NIV or continuous use of CPAP for hypoxia OR oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system	Inpatient	Dexamethasone	IV	1000	Recruiting
NCT04513184	Edda Sciutto Conde	RCT	Hospitalised patients with moderate to severe respiratory complications that have not received mechanical ventilation	Inpatient	Dexamethasone	IV vs nasal	60	Recruiting
NCT04528329	ClinAmygate	RCT	Mild to moderate severity	Unclear	Dexamethasone	Unclear, most likely systemic	300	Recruiting
NCT04528888	Massimo Girardis, University of Mod-	RCT	Included: positive pressure ventilation (IMV/NIV) for > 24 h, IMV from < 96 h, PaO2/FiO2 ratio < 150	Inpatient	Methylprednisolone	IV	210	Recruiting

Table 4. Characteristics of ongoing studies *(Continued)*

	ena and Reggio Emilia							
NCT04530409	ClinAmygate	RCT	Mild and moderate severity	Unclear	Dexamethasone	Unclear, most likely systemic	450	Recruiting
NCT04545242	Dr. Negrin University Hospital	RCT	Intubated and mechanically ventilated	Inpatient	Dexamethasone	IV	980	Not yet recruiting
NCT04636671	University of Trieste	RCT	Excluded: on IMV Included: $PaO_2 \leq 60$ mmHg or $SpO_2 \leq 90\%$ or on HFNC, CPAP or NPPV at randomisation	Inpatient	Dexamethasone, methylprednisolone	IV	680	Recruiting
NCT04663555	Brno University Hospital	RCT	Intubation/mechanical ventilation or ongoing HFNC oxygen therapy; admission to ICU	Inpatient	Dexamethasone	IV	300	Recruiting
NCT04673162	Azienda Unità Sanitaria Locale Reggio Emilia	RCT	Need for supplemental oxygen in any delivery mode with the exception of IMV	Inpatient	Methylprednisolone	IV	260	Not yet recruiting
NCT04707534	University of Oklahoma	RCT	Positive pressure ventilation (non-invasive or invasive) or HFNC or need supplemental oxygen with oxygen mask or nasal cannula	Inpatient	Dexamethasone	Unclear, most likely systemic	300	Recruiting
NCT04726098	Manuel Taboada Muñiz, Hospital Clinico Universitario de Santiago	RCT	Patients requiring supplemental oxygen	Inpatient	Dexamethasone	Unclear, most likely systemic	198	Recruiting
NCT04765371	Centre Hospitalier René Dubos	RCT	Patient with $SpaO_2 \leq 94\%$ in room air (90% for patient with respiratory failure) and requiring an oxygen therapy	Inpatient	Dexamethasone, prednisolone	Unclear, most likely systemic	220	Recruiting
NCT04780581	Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León	RCT	Requires supplementary oxygen due to basal saturation ≤ 93% (with ambient O_2, 21%) , excluded if IMV, NIV, HFNC	Inpatient	Dexamethasone, methylprednisolone	Unclear, most likely systemic	290	Recruiting

Table 4. Characteristics of ongoing studies *(Continued)*

NCT04795583	University of Alberta	RCT	Ambulatory, confirmed SARS-CoV-2. Clinical symptoms compatible with COVID-19 for ≤ 14 days before randomisation. Oxygen saturation ≥ 95%	Outpatient	Prednisone	Oral	1526	Not yet recruiting
NCT04834375	Northwell Health	RCT	Hypoxaemia defined by an oxygen saturation < 94% or the need for supplemental oxygen	Inpatient	Dexamethasone	IV	142	Recruiting
NCT04836780	Hospital Universitario Infanta Leonor	RCT	Peripheral capillary oxygen saturation (SpO_2) ≥ 94% and < 22 breaths per minute (bpm) breathing room air. High risk of developing ARDS	Inpatient	Dexamethasone	IV	126	Not yet recruiting

ARDS: acute respiratory distress syndrome; **CPAP:** continuous positive airway pressure; **CRP:** c-reactive protein; **FiO2:** fraction of inspired oxygen; **HFNC:** high-flow nasal cannula; **ICU:** intensive care unit; **IMV:** invasive mechanical ventilation; **IV:** intravenous; **LDH:** lactic dehydrogenase; **NIV:** non-invasive ventilation; **NPPV:** non-invasive positive pressure ventilation; **PaO2:** partial pressure oxygen; **PCR:** polymerase chain reaction **RCT:** randomised; controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SpO2:** blood oxygen saturation

Table 5. Characteristics of studies awaiting classification

Study	Sponsor/developer	Design	Population/disease severity	Setting	Drug	Route of administration	Number of participants	Status
EUCTR2020-001333-13-FR	Groupe Hospitalier Paris Saint-Joseph	RCT	Included: patient diagnosed COVID positive by RT-PCR and/or scanner (patients admitted with already mechanical ventilation and sedation, or with acute respiratory failure evolving very quickly)	Inpatient	Dexamethasone	IV	122	Prematurely ended
EUCTR2020-001307-16-ES	Fundación para la Investigación Biomédica Hospital Ramón y Cajal	RCT	ARDS	Inpatient	Methylprednisolone	IV	104	Prematurely ended
EUCTR2020-001553-49-FR	Hospices Civils de Lyon	RCT	Peripheral saturation by pulse oximeter SpO_2 ≤ 94% in ambient air measured	Inpatient	Prednisone	Oral	304	Prematurely ended

Table 5. Characteristics of studies awaiting classification *(Continued)*

			twice at 5-15 min intervals, or PaO_2 / FiO_2 <300 mmHg					
IRC-T20081027001451IV3	Teheran University of Medical Sciences	RCT	Blood oxygen saturation < 93%; with ARDS	Inpatient	Prednisolone	Not stated	60	Completed
IRC-T20100228003445IV3	Teheran University of Medical Sciences	RCT	With diagnosis of COVID-19 according to laboratory, clinical or radiological findings; with indication for hospitalisation	Inpatient	Dexamethasone	IV	119	Completed
IRC-T20120215009031IV4	Hamedan University of Medical Sciences	RCT	Hospitalised in ICU, bilateral pulmonary infiltration in chest X-ray or CT-scan; respiratory distress with > 24 breaths per minute	Inpatient	Hydrocortisone, methylprednisolone, dexamethasone	IV	81	Completed
IRC-T20160118026031IV4	Ghoum University of Medical Sciences	RCT	Hypoxia requires supplemental oxygen to maintain oxygen saturation > 90%	Inpatient	Dexamethasone	Not stated	64	Completed
IRC-T20200611047721IV3	Shahid Beheshti University of Medical Sciences	RCT	Oxygen saturation level < 93	Inpatient	Methylprednisolone	IV	60	Completed
IRC-T20201015049031IV1	Teheran University of Medical Sciences	RCT	Blood oxygen saturation between 90%-95%	Outpatient	Dexamethasone	Not stated	200	Completed
ISRCTN33037282	University of Trieste	RCT	$PaO_2 \leq 60$ mmHg or $SpO_2 \leq 90\%$ or on HFNC, CPAP or NPPV at randomisation Excluded: on IMV	Inpatient	Methylprednisolone, dexamethasone	IV	680	Completed

Table 5. Characteristics of studies awaiting classification *(Continued)*

NCT03852537	Mayo Clinic	RCT	Acute respiratory failure SpO_2/FiO_2 < 315 (SpO_2 < 90% on room air or < 97% on 2L NC)	Inpatient	Methylprednisolone	Not stated	44	Completed
NCT04244591	Peking Union Medical College Hospital	RCT	PaO_2/FiO_2 < 200 mmHg; positive pressure ventilation (non-invasive or invasive) or HFNC > 45 L/min for < 48 h; requiring ICU admission	Inpatient	Methylprednisolone	Not stated	80	Completed
NCT04325061	Dr. Negrin University Hospital	RCT	Intubated and mechanically ventilated	Inpatient	Dexamethasone	IV	19	Terminated (lack of enrolment)
NCT04746430	General Practitioners Research Institute	RCT	Exercise-induced desaturation, defined as SpO_2 < 92% (< 90% for COPD patients) and/or an absolute drop of ≥ 4% in SpO_2 after a 1-min sit-to-stand test or SpO_2 < 92% (< 90% for COPD patients) at rest with GP's and patient's shared decision to keep patient at home despite this in itself being an indication for referral to hospital	Outpatient	Dexamethasone	Unclear, most likely systemic	2000	Terminated (too few patients)
Munch 2021	Scandinavian Critical Care Trials Group	RCT	Severe (at least oxygen)	Inpatient	Hydrocortisone	IV	30	Terminated early (external evidence indicating benefit from corticosteroids in severe COVID-19)
Rashad 2021	South Valley University	RCT	Respiratory rate > 30 cycle/min, bilateral CT infiltration > 30%, PaO_2/FiO_2 ratio < 150 or saturation < 90 on > 6L/min	Inpatient	Dexamethasone	Unclear	69	Preprint published; methodology unclear; waiting for the full text

ARDS: acute respiratory distress syndrome; **COPD:** chronic obstructive pulmonary disease; **CT:** computed tomography; **HFNC:** high-flow nasal cannula;**ICU:** intensive care unit; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction.

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register

Search string:

corticosteroid* OR corticoid* OR prednison* OR dehydrocortison* OR deltason* OR decortin* OR orasone* OR deltra* OR meticorten* OR cortancyl* OR deltacorten* OR dacortin* OR adasone* OR "delta-cortison" OR panasol* OR decorton* OR metacortandracin* OR paracort* OR predicor* OR decortisyl* OR delta-1-cortison* OR "delta-dome" OR deltadehydrocortison* OR ofisolon* OR panafcort* OR predicorten* OR predni* OR econonson* OR promifen* OR servison* OR deltison* OR lisacort* OR meprosон* OR rayos OR sterapred* OR "liquid pred" OR cortan* OR rectodelt* OR predeltin* OR prednisolon* OR methylprednisolon* OR medrol OR "pred forte" OR medrone OR urbason OR wyacort OR "Delta-F" OR duralon* OR medrate OR omnipred OR adlone OR caberdelta OR depmedalon* OR "Depo Moderin" OR "Depo-Nisolone" OR Emmetipi OR esameton* OR firmacort OR medlon* OR "Mega-Star" OR meprolon* OR metilbetason* OR metrocort OR metypresol OR metysolon* OR orapred OR "Predni-M-Tablinen" OR radilem OR sieropresol OR solpredon* OR "A-MethaPred" OR prelone OR medrone OR aprednislon OR pediapred OR hostacortin OR "Di-Adreson-F" OR adnisolon* OR capsoid OR cortalon* OR cortisolon* OR deltacortril OR estilsona OR panafcortelone OR sterane OR "Delta-Cortef" OR econopred OR dacortin OR decaprednil OR "Delta-Diona" OR "Delta-Phoricol" OR deltahydrocortison* OR deltasolon* OR deltidrosol OR dhasolone OR fisopred OR frisolona OR gupison* OR hydeltra OR hydeltrasol OR klismacort OR kuhlprednon OR lenisolon* OR "Lepi-Cortinolo" OR "Linola-H" OR longiprednil OR metacortandralon* OR "Meti Derm" OR meticortelon* OR opredsone Or precortisyl OR "Pred-Clysma" OR predeltilon* OR prenilone OR hydrocortancyl OR "Solu Moderin" OR predonin* OR metypred OR prednisol OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR Maxidex OR Dextenza OR dexasone OR dexpak OR hydrocortison* OR cortisol OR cortef OR hydrocorton* OR cetacort OR barseb OR aeroseb OR "Cort-Dome" OR cortenema OR cortril OR cortifan OR cortispray OR dermacort OR domolene OR eldecort OR hautosone OR "Heb-Cort" OR hytone OR Komed OR Nutracort OR Proctocort OR Rectoid OR Hydrocort OR locoid OR Solu-Glyc

Study characteristics:
1) "Intervention assignment": “Randomised” OR
2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover" AND "Unclear"

Web of Science Core Collection (Advanced search)

#1 TI=(corticosteroid* OR corticoid* OR prednison* OR dehydrocortison* OR deltason* OR decortin* OR orasone* OR deltra* OR meticorten* OR cortancyl* OR deltacorten* OR dacortin* OR adasone* OR "delta-cortison" OR panasol* OR decorton* OR metacortandracin* OR paracort* OR predicor* OR decortisyl* OR delta-1-cortison* OR "delta-dome" OR deltadehydrocortison* OR ofisolon* OR panafcort* OR predicorten* OR predni* OR econonson* OR promifen* OR servison* OR deltison* OR lisacort* OR meprosон* OR rayos OR sterapred* OR "liquid pred" OR cortan* OR rectodelt* OR predeltin* OR prednisolon* OR methylprednisolon* OR medrol OR "pred forte" OR medrone OR urbason OR wyacort OR "Delta-F" OR duralon* OR medrate OR omnipred OR adlone OR caberdelta OR depmedalon* OR "Depo Moderin" OR "Depo-Nisolone" OR Emmetipi OR esameton* OR firmacort OR medlon* OR "Mega-Star" OR meprolon* OR metilbetason* OR metrocort OR metypresol OR metysolon* OR orapred OR "Predni-M-Tablinen" OR radilem OR sieropresol OR solpredon* OR "A-MethaPred" OR prelone OR medrone OR aprednislon OR pediapred OR hostacortin OR "Di-Adreson-F" OR adnisolon* OR capsoid OR cortalon* OR cortisolon* OR deltacortril OR estilsona OR panafcortelone OR sterane OR "Delta-Cortef" OR econopred OR dacortin OR decaprednil OR "Delta-Diona" OR "Delta-Phoricol" OR deltahydrocortison* OR deltasolon* OR deltidrosol OR dhasolone OR fisopred OR frisolona OR gupison* OR hydeltra OR hydeltrasol OR klismacort OR kuhlprednon OR lenisolon* OR "Lepi-Cortinolo" OR "Linola-H" OR longiprednil OR metacortandralon* OR "Meti Derm" OR meticortelon* OR opredsone Or precortisyl OR "Pred-Clysma" OR predeltilon* OR prenilone OR hydrocortancyl OR "Solu Moderin" OR predonin* OR metypred OR prednisol OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR Maxidex OR Dextenza OR dexasone OR dexpak OR hydrocortison* OR cortisol OR cortef OR hydrocorton* OR cetacort OR barseb OR aeroseb OR "Cort-Dome" OR cortenema OR cortril OR cortifan OR cortispray OR dermacort OR domolene OR eldecort OR hautosone OR "Heb-Cort" OR hytone OR Komed OR Nutracort OR Proctocort OR Rectoid OR Hydrocort OR locoid OR Solu-Glyc) OR AB=(corticosteroid* OR corticoid* OR prednison* OR dehydrocortison* OR deltason* OR decortin* OR orasone* OR deltra* OR meticorten* OR cortancyl* OR deltacorten* OR dacortin* OR adasone* OR "delta-

cortison" OR panasol* OR decorton* OR metacortandracin* OR paracort* OR predicor* OR decortisyl* OR delta-1-cortison* OR "delta-dome" OR deltadehydrocortison* OR ofisolon* OR panafcort* OR predicorten* OR predni* OR econonson* OR promifen* OR servison* OR deltison* OR lisacort* OR meprosn* OR rayos OR sterapred* OR "liquid pred" OR cortan* OR rectodelt* OR predeltin* OR prednisolon* OR methylprednisolon* OR medrol OR "pred forte" OR medrone OR urbason OR wyacort OR "Delta-F" OR duralon* OR medrate OR omnipred OR adlone OR caberdelta OR depmedalon* OR "Depo Moderin" OR "Depo-Nisolone" OR Emmetipi OR esameton* OR firmacort OR medlon* OR "Mega-Star" OR meprolon* OR metilbetason* OR metrocort OR metypresol OR metysolon* OR orapred OR "Predni-M-Tablinen" OR radilem OR sieropresol OR solpredon* OR "A-MethaPred" OR prelone OR medrone OR aprednislon OR pediapred OR hostacortin OR "Di-Adreson-F" OR adnisolon* OR capsoid OR cortalon* OR cortisolon* OR deltacortril OR estilsona OR panafcortelone OR sterane OR "Delta-Cortef" OR econopred OR dacortin OR decaprednil OR "Delta-Diona" OR "Delta-Phoricol" OR deltahydrocortison* OR deltasolon* OR deltidrosol OR dhasolone OR fisopred OR frisolona OR gupison* OR hydeltra OR hydeltrasol OR klismacort OR kuhlprednon OR lenisolon* OR "Lepi-Cortinolo" OR "Linola-H" OR longiprednil OR metacortandralon* OR "Meti Derm" OR meticortelon* OR opredsone Or precortisyl OR "Pred-Clysma" OR predeltilon* OR prenilone OR hydrocortancyl OR "Solu Moderin" OR predonin* OR metypred OR prednisol OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR Maxidex OR Dextenza OR dexasone OR dexpak OR hydrocortison* OR cortisol OR cortef OR hydrocorton* OR cetacort OR barseb OR aeroseb OR "Cort-Dome" OR cortenema OR cortril OR cortifan OR cortispray OR dermacort OR domolene OR eldecort OR hautosone OR "Heb-Cort" OR hytone OR Komed OR Nutracort OR Proctocort OR Rectoid OR Hydrocort OR locoid OR Solu-Glyc)

#2 TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3 #1 AND #2

#4 TI=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

#5 #3 AND #4

Indexes=SCI-EXPANDED, ESCI Timespan=2020-2021

WHO COVID-19 Global literature on coronavirus disease

(corticosteroid* OR corticoid* OR prednis* OR hydrocorti* OR methylpredni* OR deltahydrocorti* OR dehydrocorti* OR dexameth* OR desameth*) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

CONTRIBUTIONS OF AUTHORS

CW: screening, data extraction, risk of bias assessment, meta-analysis, writing of the review, consulting with Cochrane Methodological Support, taking responsibility for reading and checking the review before submission

MG: data extraction, risk of bias assessment, meta-analysis, conception and writing of the review, contacting corresponding authors for additional information, consulting with Cochrane Methodological Support, taking responsibility for reading and checking the review before submission

AM: extraction, clinical expertise, writing of the review, taking responsibility for reading and checking the review before submission

AMu: clinical expertise, writing of the review, taking responsibility for reading and checking the review before submission

MIM: design and conduct of searches, drafting of search methods section, taking responsibility for reading and checking the review before submission

ALF: extraction, characteristics of ongoing studies, writing of the review, taking responsibility for reading and checking the review before submission

MK: risk of bias assessment, writing of the review, taking responsibility for reading and checking the review before submission

MN: characteristics of studies awaiting classification, writing of the review, taking responsibility for reading and checking the review before submission

MS: clinical expertise, writing of the review, securing the funding, taking responsibility for reading and checking the review before submission

KK: extraction, taking responsibility for reading and checking the review before submission

NS: screening, methodological expertise and advice, conception and writing of the review, securing the funding, characteristics of studies awaiting classification, taking responsibility for reading and checking the review before submission

FF: clinical expertise, writing of the review, meta-analysis, securing the funding, taking responsibility for reading and checking the review before submission

DECLARATIONS OF INTEREST

CW: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'CEOSys', which was paid to the institution).

MG: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'CEOSys', which was paid to the institution); works as a resident with the Department of Anaesthesiology and Intensive Care at the University of Leipzig Medical Center; is member of the German Society for Anaesthesia and Intensive Care.

AM: works as a physician at the Department of Infectious Diseases and Respiratory Medicine at Charité University medicine Berlin; is a member of the German Society for Infectious Diseases; works in the office of STAKOB at Robert Koch-Institut; coordinates the work of the specialist group COVRIIN.

AMu: none known.

MM: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'CEOSys', which was paid to the institution).

AF: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'CEOSys', which was paid to the institution) and works as a resident with the Department of Anaesthesiology and Intensive Care at the University of Leipzig Medical Center.

MK: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'CEOSys', which was paid to the institution).

MN: works as a health professional; Leadership or other fiduciary role in other board, society, committee, or advocacy group; Published opinions in medical journals, the public press, broadcast and social media relevant to the interventions in the work.

MS: none known.

KK: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'CEOSys', which was paid to the institution); works as an intensive care specialist with the Department of Anaesthesiology and Intensive Care at the University of Leipzig Medical Center; is a member of the German Society for Anaesthesia and Intensive Care.

NS: none known.

FF: works as an intensive care consultant with the Department of Anaesthesiology and Intensive Care at the University of Leipzig Medical Center and is a member of the CEOsys project (no direct funding), the German Society for Anaesthesia and Intensive Care (DGAI), and the German Interdisciplinary Association for Intensive and Emergency Medicine (DIVI). Leading role in German guideline on respiratory failure and invasive mechanical ventilation.

SOURCES OF SUPPORT

Internal sources

- University Hospital of Cologne, Germany

  Cochrane Cancer, Department I of Internal Medicine
- Leipzig University Hospital, Germany

  Department of Anaesthesiology and Intensive Care

External sources

- Federal Ministry of Education and Research, Germany

  NaFoUniMedCovid19“ (funding number: 01KX2021) part of the project „CEO-Sys“

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants

For the different endpoints of interest and treatment settings, we excluded participants treated for symptoms of long-COVID. Still, treatments for long-COVID should soon be addressed outside this review.

Types of outcome measures

For heterogeneous reporting and high bias through death as competing risk, we omitted most endpoints with regard to clinical improvement and worsening, and length of hospital stay. As a compromise and because of their importance for the patients, or a rather easy ascertainment or strong implication for resource usage, we kept in the first publication of this living review: new need for invasive ventilation, liberation from invasive ventilation, ventilator-free days, need for dialysis, viral clearance, quality of life/neurological outcome.

We counted adverse events regardless of their grades because the included studies did not report grades of adverse events.

If not specified otherwise, the observation period for outcomes other than mortality was the longest period available. Where this differed between arms of a trial, risk of bias assessment would be adjusted.

Types of intervention

After discussion with clinical experts we added comparisons to meet questions arising in daily routine:

- dose comparisons
- time comparisons (early versus late) but indirectly in terms of disease severity as described below
- two different types of corticosteroids
- corticosteroid versus another active substance (e.g. remdesivir, tocilizumab)

On the other hand, we excluded topical and inhaled steroids from this review because of inherently different pharmacokinetics and treatment settings. Still, their role is critical and should soon be addressed in another review.

Analysis

We made calculations with RevMan Web instead of RevMan 5.4 software.

We omitted subgroup analysis for treatment settings, that is, outpatient, inpatient, and intensive care unit, because triage criteria, definition of intensive care or high-dependency units, and available resources were deemed too heterogeneous. Taking away a degree of indirectness, we instead performed subgroup analysis stratified by the level of respiratory support needed at randomisation. This allowed for the fact that levels of respiratory support can at least partially be delivered independent of the treatment setting and hence rendered a more valid conclusion about disease severity.

NOTES

Parts of the review's methods section and of the background were adopted from Cochrane Haematology templates (Kreuzberger 2021; Piechotta 2021).

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; COVID-19 [diagnosis] [*drug therapy]; Immunization, Passive; Randomized Controlled Trials as Topic; Respiration, Artificial; SARS-CoV-2

MeSH check words

Humans