CADTH COVID-19 PANDEMIC

COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

Systemic Corticosteroids for the Management of COVID-19: A Review of Clinical Effectiveness

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To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

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Abbreviations

AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews
ARDS	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
CRD	Centre for Reviews and Dissemination
FiO_2	fraction of inspired oxygen
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICU	Intensive Care Unit
IQR	interquartile range
MERS	Middle East Respiratory Syndrome
MeSH	Medical Subject Headings
n	subsample size
PaO_2	partial pressure of oxygen
RT-PCR	reverse transcriptase polymerase chain reaction
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome-related Coronavirus 2
SD	standard deviation
SOFA	Sequential Organ Failure Assessment
SpO_2	oxygen saturation
SR	systematic review
RCT	randomized controlled trial
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
WHO	World Health Organization

Context and Policy Issues

The coronavirus disease identified in 2019 (COVID-19) is an infection of the respiratory tract caused by the Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2).[1,2] Since the World Health Organization (WHO) declared COVID-19 as a pandemic in March, 2020,[3] the disease has spread globally and is one of the major public health concerns in recent history. As of October 5, 2020 there were 35,274,993 cases of COVID-19 confirmed globally, and 1,038,534 confirmed deaths attributed to COVID-19.[4] In Canada, there were 173,123 cases and 9,541 deaths as of October 8, 2020.[5] Among those who develop COVID-19, most people have few- to no symptoms of the disease.[1,6]

Approximately fourteen percent of people identified as having COVID-19 require hospitalization and five percent are admitted to an intensive care unit (ICU).[1]

Clinical trials are currently underway to identify treatment options for COVID-19.[7-9] Current management strategies include symptomatic care, oxygen support (nasal cannula, invasive and non-invasive mechanical ventilation) along with experimental use of antivirals, empirical antibiotics, intravenous immunoglobulins, convalescent plasma, corticosteroids, and other drugs.[1,6] Preliminary results from a randomized trial in the UK (RECOVERY trial), published in July 2020, showed that the use of dexamethasone resulted in lower mortality among patients with severe illness receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support.[10] On September 2, 2020 WHO published an interim clinical practice guideline on the use of corticosteroids for COVID-19 based on prospective meta-analysis data from ongoing randomized clinical trials.[7] WHO issued a strong recommendation (based on moderate certainty evidence) for the use of corticosteroids versus no corticosteroids for the treatment of patients with severe and critical COVID-19. They also suggest not to use corticosteroids for the treatment of patients with non-severe COVID-19 (conditional recommendation, low certainty evidence).[1,7]

The objective of this report is to summarize the evidence regarding the clinical effectiveness of systemic corticosteroids for the management of COVID-19.

Research Question

What is the clinical effectiveness of systemic corticosteroids for the management of individuals with coronavirus disease (COVID-19)?

Key Findings

Five systematic reviews and four RCT were identified regarding the clinical effectiveness of systemic corticosteroids for the management of individuals with COVID-19. The evidence was of limited quality, and findings were inconclusive regarding the effectiveness of systematic corticosteroids with respect to mortality, patient symptoms, or medical care outcomes in patients with COVID-19. Adverse events were not assessed in six of the included studies (three primary studies, three systematic reviews); in the three studies that did quantify adverse events (one primary, two systematic reviews), no differences between treatment groups were identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were systemic steroids and COVID-19. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2018 and September 17, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals with confirmed or suspected COVID-19
Intervention	Intravenous or oral systemic corticosteroids (e.g., hydrocortisone, dexamethasone, prednisone, methylprednisolone) alone or in combination with other therapies)
Comparators	No treatment; placebo; standard care; other active treatments (e.g., remdesivir)
Outcomes	Clinical effectiveness (e.g., mortality, length of hospital stay, severity of clinical symptoms, viral load, safety [e.g., adverse events])
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2018.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2),[11] and randomized studies were critically appraised using Downs and Black checklist.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 541 citations were identified in the literature search. Following screening of titles and abstracts, 515 citations were excluded and 26 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles,19 publications were excluded for various reasons. One prospective meta-analysis[13] was excluded because it included interim unpublished data from ongoing trials. Nine publications met the inclusion criteria and were included in this report. These comprised five systematic reviews (SR)[14-18] and four randomized controlled trials (RCTs).[19-22] Appendix 1: Selection of Included Studies presents a flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Three[14,17,18] of the five SRs had broader inclusion criteria than the present review, as they included studies in patients with severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) in addition to those with COVID-19. Only the characteristics and results of the subset of relevant studies are described in this report.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Five SRs[14-18] – four with meta-analysis[14,15,17,18] – that were published in 2020 were included in this report. All SR authors searched for and included primary RCTs and observational studies. Authors of all included SRs searched multiple electronic databases to identify eligible primary studies. Three SRs[14,15,18] included preprints and meta-analyses in addition to peer-reviewed published studies. Lu et al.[14] searched for eligible publications from January 1, 2003 to March 31, 2020. The SR included 23 studies, among which, five were relevant to the current report. Sarkar and colleagues[15] conducted their search from January 1 to August 19, 2020. The SR included 15 RCTs and cohort studies. Veronese et al.[16] searched for studies from database inception to March 15, 2020 and identified four primary studies. Ye and colleagues[18] conducted a literature search from database inception to April 25, 2020 and included 35 primary studies, among which six were relevant to the current report. Lastly, Yang et al.[17] searched for retrospective observational studies from January 1, 2002 to March 15, 2020 and included no primary studies relevant to the current report.

The four primary clinical studies included in this report were RCTs.[19-22] The CAPE-COVID trial conducted by Dequin et al.[19] was a multicenter, double-blind, sequential trial conducted from March 7, 2020 to June 7, 2020. The Metcovid study by Jeronimo et al.[20] was a parallel, double-blind, Phase IIb clinical trial conducted from April 18 to June 16, 2020. The third RCT, the CoDEX trial by Tomazini et al.,[21] was an open-label trial conducted from April 17 to June 23, 2020. Lastly, the REMAP-CAP trial[22] is an ongoing multi-factorial (evaluates several treatment options simultaneously), open-label trial, embedded in routine care for pneumonia, that uses an adaptive platform whereby the intervention(s) evolve over time (e.g., in the event of pandemics or as new information is learned from interim analysis). . Patients were enrolled to examine the domain of relevance to this report (i.e., the corticosteroid domain) from March to June 2020.The characteristics and results of the corticosteroid domain are summarized in the current report.

Country of Origin

The included SRs were conducted by authors from Canada,[18] China,[14,17] India,[15] and Italy.[16]

The REMAP-CAP[22] RCT was conducted at multiple sites across several countries, namely Australia, Canada, France, Ireland, the Netherlands, New Zealand, UK, and US. The other RCTs were conducted in Brazil[20,21] and France.[19]

Patient Population

The population of interest for the included SRs was patients with COVID-19.[14-18] The number of participants from the relevant primary studies ranged from 542[16] to 15,754.[15] The mean age of study participants ranged from 48.7 to 56.3 years in one SR[14] and was 52 years in another;[16] less than half of participants in these SRs were women. Two other included SRs[15,18] did not report the mean age or the sex distribution of the population sample.

The CAPE-COVID[19] trial enrolled adult patients with confirmed or suspected COVID-19 who were admitted to the ICU. Patients also needed to fulfill at least one of the following four disease severity criteria to be considered eligible for the trial: 1) mechanical ventilation with a positive end-expiratory pressure of 5 cm H_2O or more; 2) ratio of partial pressure of

oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) < 300 on high-flow oxygen therapy, with an FiO_2 of ≥ 50%; 3) supplemental oxygen with a PaO_2:FiO_2 ratio < 200 (estimated using prespecified charts; or 4) pulmonary severity index > 130. Patients with septic shock (treated by vasopressors), hypersensitivity to corticosteroids, need for corticosteroids for other indication, active infections (e.g., tuberculosis, fungal infection, viral hepatitis), or do not intubate orders were excluded. Patients who were receiving steroids (for > 30 days) at baseline or those who were pregnant or lactating were also excluded. Based on these criteria the study enrolled 143 participants (hydrocortisone group, n = 76; placebo group, n = 73) with a median age of 63.1 (IQR [interquartile range], 51.5 to 70.8) years and 66.3 years (IQR, 53.5 to 72.7) in the hydrocortisone group and placebo group respectively.

The Metcovid trial[20] enrolled adult patients (≥ 18 years of age) with clinically or radiologically suspected COVID-19 who had an oxygen saturation (SpO_2) ≤ 94% in room air or were on supplementary oxygen or under mechanical ventilation. Clinical criteria included history of fever and any respiratory symptoms, and radiological criteria included ground glass opacity or pulmonary consolidation on computed tomography scan. Patients with known hypersensitivity to methylprednisolone, HIV/acquired immunodeficiency syndrome, chronic use of corticosteroids or immunosuppressants, decompensated cirrhosis, or chronic renal failure were excluded. Pregnant or lactating patients were also excluded. Based on these criteria the trial enrolled 393 participants (treatment group, n = 194; placebo group, n = 199) with a mean age of 54 years (standard deviation, SD = 15) in each group.

The CoDEX trial[21] enrolled adult patients with acute respiratory distress syndrome (ARDS) who were admitted to the ICU due to confirmed or probable COVID-19. Exclusion criteria were pregnancy or active lactation, known hypersensitivity to dexamethasone, use of dexamethasone in the last 15 days (among non-hospitalized patients), other use of corticosteroids or immunosuppressive drugs, neutropenia, or imminent death. The trial enrolled 299 patients (dexamethasone group, n = 151; control group, n = 148) with a mean age of 61 years (SD = 14).

Lastly, the REMAP-CAP trial[22] enrolled adult patients with presumed or confirmed SARS-CoV-2 infection with severe illness and admitted to the ICU for cardiovascular or respiratory organ support. Respiratory organ support was defined as either invasive or non-invasive mechanical ventilation or high-flow oxygen through nasal cannula with a flow rate ≥30 litres per minute or FiO_2 ≥ 0.4. Cardiovascular organ support was defined as intravenous infusion of vasopressor or inotrope. Patients with hypersensitivity to hydrocortisone, systemic steroid use at baseline, ICU admission > 36 hours prior to baseline, or those who were likely to be administered corticosteroids for reasons unrelated to COVID-19, or imminent death were excluded from the trial. The trial enrolled 403 patients (fixed-dose hydrocortisone, n = 137; shock-dependent hydrocortisone, n = 146; No hydrocortisone, n = 101). The mean ages of the participants were 60.4 years (SD = 11.6) in the fixed-dose hydrocortisone group, 59.5 years (SD = 12.7) in the shock-dependent hydrocortisone group and 59.9 years (SD = 14.6) in the no hydrocortisone group.

Interventions and Comparators

The interventions of interest for the included SRs[14-18] were systemic corticosteroids for the management of COVID-19. Lu and colleagues[14] also specified that they considered a combination of glucocorticoids and symptomatic care as the intervention of interest. The comparator for all five SRs was non-administration of steroids (standard care).

In the CAPE-COVID trial,[19] the intervention was intravenous hydrocortisone with an initial dose of 200 mg/day as a continuous infusion. The treatment course was administered as 200 mg/day for the first 7 days, followed by 100 mg/day for 4 days, and 50 mg/day for 3 days (14 days in total). For patients whose general and respiratory status was improved by day 4, a shorter course was administered: 200 mg/day for the first 4 days, 100 mg for 2 days, and 50 mg/day for the next two days (8 days in total). Treatment with steroids was stopped for all patients on discharge from the ICU. The comparator was a placebo (saline solution).

In the Metcovid trial,[20] sodium succinate methyl prednisolone was administered at a dosage of 0.5 mg/kg twice daily for five days to patients in the treatment group. The comparator was a placebo (saline solution). All patients with ARDS were also administered antibiotics.

In the CoDEX trial,[21] 20 mg/day intravenous dexamethasone was administered for five days followed by 10 mg/day until discharge from the ICU, in addition to standard care. The comparator was standard care alone.

In the REMAP-CAP trial,[22] participants were divided into three groups based on the treatment they received. In the fixed-dose group, 50 mg intravenous hydrocortisone was given to patients every 6 hours for 7 days. In the shock-dependent group, patients received 50 mg intravenous hydrocortisone every 6 hours while in shock for up to 28 days. No hydrocortisone or other corticosteroids were given to those in the comparator group. It was noted that patients in all groups could receive steroids for non-COVID related indications such as bronchospasm, anaphylaxis or post-extubation stridor. By the end of the study 15% of patients in the no hydrocortisone group had received at least one dose of systemic steroids.

Outcomes

The primary outcome for four of the SRs[14,15,17,18] was mortality, while the fifth SR[16] considered all health outcomes associated with corticosteroid treatment. Secondary outcomes that were considered in the SRs included duration of hospital stay,[14,15,17] duration of viral shedding,[15,18] duration of lung inflammation absorption,[14] duration of fever,[14] and ICU admission.[18] The definition of the outcome duration of lung inflammation absorption was unclear from the SR.[14] Adverse events were outcomes of interest in two SRs.[14,17] Follow-up duration in the included primary studies was not reported in any of the SRs.[14-18]

The primary outcome in the CAPE-COVID trial[19] was treatment failure on day 21, defined as death or continued dependency on mechanical ventilation or high-flow oxygen therapy. Secondary outcomes included proportion of patients with nosocomial infections and adverse events. Patients were followed for 21 days for all outcomes except nosocomial infection, for which follow-up was 28 days (post-hoc decision).

The primary outcome in the Metcovid trial[20] was 28-day mortality. The secondary outcomes included mortality at day 7 and 14, need for orotracheal intubation by day 7, and the proportion of patients with PaO_2:FiO_2 ratio < 100 on day 7. The participants were followed for 28 days.

The primary outcome in the CoDEX trial[21] was 28-day ventilator-free days, defined as the number of days alive and not dependent on mechanical ventilation for a minimum of 48 consecutive hours. Patients who were discharged before 28 days were considered ventilator free at 28 days, whereas patients who died before 28 days were considered to have no ventilator free days. Secondary outcomes included 28-day all-cause mortality,

clinical status at day 15 (assessed using the 6-point disease severity scale by WHO, ranging from 1 [not hospitalized] to 6 [death]), ICU-free days, duration of mechanical ventilation, and organ failure assessed using sequential organ failure assessment (SOFA) scores. The SOFA scores range from 0 to 24, with a higher score indicating greater organ dysfunction. SOFA was assessed at 48 hours, 72 hours, and 7 days. Patients in the trial were followed for 28 days or until discharge, whichever came first.

The primary outcome in the REMAP-CAP trial[22] was respiratory and cardiovascular organ support-free days. Respiratory organ support was defined as either invasive or non-invasive mechanical ventilation or high-flow oxygen through nasal cannula with a flow rate ≥ 30 L/minute or FiO_2 ≥ 0.4. Cardiovascular organ support was defined as intravenous infusion of vasopressor or inotrope. Secondary outcomes included time to death, duration of ICU stay, duration of hospital stay, cardiovascular organ support-free days, respiratory organ support-free days, and disease status at day 14 (assessed using the WHO ordinal scale ranging from 0 [no illness] to 8 [death]). Patients were followed for 21 days

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The five SR[14-18] authors described the objectives and inclusion criteria for the reviews, and included the components of population, intervention, comparators and outcomes of interest. Authors of one of the SRs reported that they had established their protocol prior to the conduct of the review.[18] The authors of all five SRs conducted comprehensive literature searches involving multiple electronic databases and detailed search strategies were reported.[14-18] Reference lists of selected articles were hand-searched for potential additional studies in three SRs.[14,16,17] In all reviews, study selection and data extraction from the selected studies were done independently by two reviewers, lowering risk of errors.[14-18] In four SRs, authors conducted quality assessments of the included primary studies using validated tools. Specifically, the Newcastle-Ottawa scale (three SRs),[14,17,18] Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) (one SR)[15] for observational studies, and Cochrane risk of bias tool for RCTs (two SRs).[14,15] Four SRs[14,15,17,18] conducted meta-analyses to quantitatively synthesize results from the primary studies. Appropriate statistical techniques were used to conduct the meta-analyses, and heterogeneity was assessed using the I^2 statistic in the four SRs.[14,15,17,18] Heterogeneity and risk of bias were considered while interpreting and discussing the results of the analyses in the four SRs.[14,15,17,18] The quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool in two SRs.[14,15] The quality of the evidence from these SRs was reported as ranging from very low to low. Three of the SRs assessed publication bias using valid techniques, and showed publication bias was unlikely.[14,15,17]

As for the limitations, review methods and protocols were not registered a priori for two of the SRs due to time constraints.[14,15] It was unclear whether protocols were established a priori for two other SRs.[16,17] None of the included SRs provided a list of excluded studies or reasons for exclusion.[14-18] Three SRs[14,15,18] included non-peer-reviewed data from preprint publications. Because of the limitations of preprint publications (e.g., uncertain trustworthiness, findings may change from preprint to final published versions), including data from preprints lowered the internal validity of the analyses. One SR, in which data

were synthesized narratively (no meta-analysis), did not assess the risk of bias within the primary studies, which lowered the internal validity of the review.[16] In one SR, the definition of "duration of lung inflammation absorption" was not clearly defined.[14] In the SR by Sarkar and colleagues,[15] demographic characteristics (e.g., mean age, sex) of participants in primary studies were not reported. The meta-analyses of two SRs had high heterogeneity; however, the sources of heterogeneity were not discussed.[14,15] The author of one SR declared a conflict of interest as being an investigator in a trial evaluating the effect of corticosteroids in COVID-19, but it was unclear whether this was addressed and resolved.[18]

Randomized Controlled Trials

The authors of four RCTs included in this report described their study objectives clearly and provided details regarding the inclusion criteria, interventions (dosage, administration and duration), comparators, and outcomes. The trial protocols were established and registered a priori and all of the trials used randomized allocation to assign participants to treatment groups.[19-22] Two studies were designed as double-blinded RCTs with allocation concealment.[19,20] Randomized allocation and blinding increased the internal validity of these studies. All trials reported detailed characteristics of patients for the overall sample.[19-22] Study findings were clearly described in the form of simple outcome data. Intention-to-treat analysis was conducted in two trials,[20,21] and in one RCT[19] missing outcome data were conservatively considered as treatment failure. Estimates of random variability were provided, such as confidence intervals, SDs, or IQRs.[19-22] Three RCTs[19,21,22] measured and reported important adverse events that may be a consequence of the intervention; however, adverse events in the comparator groups were also reported in only two of these trials.[19,22] All trials were conducted in centres where staff, places, and facilities were likely to be representative of the treatment the majority of patients receive. Two RCTs[19,21,22] were multicenter and one[22] was multinational and multicenter increasing the external generalizability of the results.

The main limitation of the RCTs was that three of the RCTs[19,21,22] were terminated early when preliminary results from the RECOVERY[10] trial (captured in this report through inclusion in a SR[15]) showed improved 28-day mortality with dexamethasone, leading researchers to determine it was not ethical to continue their trials. Accordingly, two RCTs[19,22] did not enrol enough study participants to ensure adequate statistical power. Since between-group statistical comparisons of participant baseline characteristics were not reported in two trials, it was unclear whether potential confounders were equally distributed between the groups.[19,20] The Metcovid trial did not report the incidence of adverse events in the intervention and control groups.[20] In the CoDEX trial,[21] the inclusion and exclusion criteria for study participation was changed after 182 patients had been enrolled, to better reflect the practical realities of treating COVID-19 patients in Brazil (e.g., the timing of admission to ICU was changed, as patients frequently receive an ARDS diagnosis and are placed on a ventilator prior to ICU admission due to ICU bed shortages in Brazil; patients were allowed to have been receiving corticosteroids at time of recruitment due to the wide-spread use of corticosteroids in hospitals in Brazil). It is possible that patients enrolled before and after the amendment were systematically different. However, the changes made to the protocol would be expected to bias the results toward the null if bias were introduced. The validity of, and minimal clinically important difference in the SOFA scores were not reported by the study authors.

The REMAP-CAP trial[22] had some additional methodological and reporting limitations. First, the analytical model assumed proportional effects across the primary outcome (organ support-free days). However, it was unclear whether this assumption was formally

assessed and met. Second, study participants were permitted to participate in multiple intervention domains within the broader trial and the primary analysis of the study included all participants. The analysis of relevance to this report (i.e., the comparison of participants treated with corticosteroids and those without) did not account for co-interventions, and these may have been imbalanced between intervention and comparison group. Thus, it was possible that the observed results were influenced by other interventions received by the patients. Third, it is difficult to interpret the clinical relevance of study findings due to the definition of the primary outcome. A composite variable labelled "respiratory and cardiovascular support-free days" included death as part of the composite (death labelled as -1, being the worst outcome). It is not clear why alternative approaches to analyzing these outcomes independently (e.g., a competing risk model) were not used Fourth, the early termination of the study left the analysis underpowered. Lastly, fifteen percent of the patients in the control group (no hydrocortisone group) received systemic hydrocortisone for other indications, increasing the likelihood of bias toward smaller effect sizes.

For all RCTs, it was possible that participants in intervention and control groups received standard care and other concomitant medications and that the use of these medications affected the patient outcomes. Lastly, the authors of three RCTs[19,21,22] declared multiple conflicts of interests in the form of funding from pharmaceutical companies, grants and participation in other COVID-19 steroid trials. It was unclear whether these potentially relevant conflicts were addressed or resolved.

Summary of Findings

Clinical Effectiveness of Systemic Corticosteroids

Mortality

Mortality was examined in four SRs,[14-16,18] and three RCTs.[19-21]

The review authors reported inconsistent findings. Two meta-analyses showed higher mortality for patients treated with corticosteroids as compared to standard care (in a synthesis of twelve studies by Sarkar and colleagues,[15] and two studies in patients with severe illness by Ye and colleagues[18]). The between-group differences identified by Sarkar et al. were not significant in subgroup analyses for patients with mild illness, patients with critical illness, patients treated with low doses of corticosteroid, or patients treated with high doses of corticosteroid, potentially due to a lack of statistical power.[15] Similarly, Lu and colleagues reported no difference in the risk of mortality with systemic corticosteroids versus non-steroid treatment based on meta-analysis of data from five studies.[14] In contrast, patients with COVID-19 and ARDS who were treated with methyl prednisone had statistically significantly lower mortality than patients treated with usual care in one included primary study within the SR.[18]

Findings from narratively synthesized results were inconsistent as well. One observational study that was not included in the meta-analysis in the SR by Ye et al.[18] showed a significantly greater "mortality composite outcome or ICU admission" for patients with mixed severity COVID-19 who were treated with a corticosteroid versus those who were not. In contrast, authors of one observational study in patients with COVID-19 and ARDS that was included in the review by Veronese and colleagues[16] reported a statistically significantly lower risk of death in those treated with methyl prednisone versus usual care.

There were mixed favourable and null findings regarding mortality and the use of steroids in the included RCTs.[20,21] Three of the four RCTs showed null findings. Specifically, there

were no significant differences between low-dose hydrocortisone and placebo groups for treatment failure on day 21 (defined as death or continued dependency on mechanical ventilation or high-flow oxygen therapy) in the CAPE-COVID trial,[19] between methyl prednisone and placebo groups for mortality at 7-, 14-, or 28-days for the overall sample of patients in the Metcovid trial,[20] and steroid treatments (fixed-dose or shock-dependent hydrocortisone) were not superior to the non-steroid comparator in the REMAP-CAP trial for time to death.[22] However, post-hoc analysis of patients over 60 years of age in the Metcovid trial showed significantly lower 28-day mortality for those treated with methyl prednisone (46% mortality) versus placebo (61.9% mortality).[20] The CoDEX trial also produced favourable findings, where participants in the dexamethasone plus standard care treatment group had a mean of approximately 2.5 additional days alive and ventilator free than the standard care comparator group when examined at 28 days.[21]

Organ Support

Randomized trials reported no difference between steroid and non-steroid groups for duration of mechanical ventilation (CoDEX trial), need for invasive mechanical ventilation until day seven (Metcovid trial),[20] or the proportion of patients with oxygenation index (PaO_2/FiO_2) <100 until day seven (Metcovid trial).[20] Additionally, the REMAP-CAP trial demonstrated non-superiority of steroid intervention groups versus comparators for cardiovascular support-free days, organ support-free days, and respiratory support-free days.[22]

Sequential Organ Failure Assessment

In the CoDEX trial, there was no difference between dexamethasone plus standard care versus standard care alone on adjusted SOFA scores for the prediction of mortality in COVID-19 patients when assessed at 48 hours, 72 hours, 7 days, or day 15.[21]

Pulmonary Fibrosis

There was no difference between methyl prednisone and placebo groups for pulmonary fibrosis when assessed after day seven in the Metcovid trial.[20]

Bronchiolitis Obliterans with Organizing Pneumonia

There was no difference between methyl prednisone and placebo groups for bronchiolitis obliterans with organizing pneumonia when assessed after day seven in the Metcovid trial.[20]

Duration of Fever

One SR showed there were approximately three fewer days of fever in the corticosteroid group versus no corticosteroid in one included observational study of 46 people.[14]

Viral Shedding

Viral shedding was examined in two SRs, which showed conflicting findings. Prolonged viral shedding with steroid use versus no steroid use was found in a meta-analysis of two observational studies,[18] while no significant difference between steroid and no steroid treatment was shown in a second meta-analysis of two observational studies.[15]

Presence of Viral RNA

One study included in the SR by Veronese et al. examined the duration of viral RNA detection for oropharyngeal swabs and feces and showed duration in the corticosteroid

treatment group was longer than that in the non-corticosteroid treatment group.[16] In contrast, authors of the Metcovid trial reported that the presence of viral RNA in the naso/oropharyngeal swab did not differ between methyl prednisone or placebo groups on treatment day five or seven.[20]

Length of Hospital Stay or ICU Admission

All four SRs[14,15,17,18] and three RCTs[20-22] examined hospitalization-related outcomes.

Authors of one study included in the SR by Veronese and colleagues examined ICU admissions, and observed that patients with COVID-19 and associated pneumonia who were treated with glucocorticoid therapy had a significantly greater percentage of ICU admissions compared to those who did not receive glucocorticoid therapy.[16]

Regarding length of hospital stay, there was no difference between steroid and non-steroid comparator groups in a meta-analysis of six trials.[15] In contrast, a meta-analysis of two observational studies showed that treatment with glucocorticoids was associated with approximately two more days in hospital than the non-steroid comparator.[14]

Authors of the RCTs showed there was no significant difference in hospitalization between corticosteroid intervention groups and non-corticosteroid comparison groups in the Metcovid and REMAP-CAP trials,[20,22] or ICU-free days in the CoDEX or REMAP-CAP trials.[21,22]

Lung Inflammation Absorption Time (Days)

One SR showed no statistically significant difference between steroid and non-steroid groups with regard to lung inflammation absorption time.[14]

Adverse Events

In the two SRs that examined adverse events, no adverse events were reported. [14,17]

Among the RCTs, nosocomial infections did not differ significantly between groups in the CAPE-COVID trial on day 28.[19] Authors of the CoDEX trial reported no significant differences between dexamethasone and standard care groups for serious adverse events, new diagnosis of infection by day 28, ventilator-associated pneumonia, catheter-related blood stream infection, catheter-associated urinary tract infections, bacteremia, insulin use for hyperglycemia, or “other” adverse effects.[21] Authors of the Metcovid trial reported no adverse events for either the steroid or intervention group.[20]

A list of single serious adverse events that were reported but not assessed statistically in the CAPE-COVID trial[19] and REMAP-CAP trial[22] can be found in Appendix 4 in a table of the main study findings and authors’ conclusions.

Limitations

This report is not without limitations. The scientific world is still in the early stages of understanding the COVID-19 pandemic, and active research has been continuing to identify possible therapies for the disease. Although the current report identified five SRs and four RCTs evaluating the effectiveness of systemic corticosteroid therapy for COVID-19, there are several ongoing research trials. It is possible that the results from well-designed RCTs may be different from the findings of this report. The literature searches of four SRs[14,16-18] were conducted early in the pandemic, and captured records published up to April 2020, which precluded them from including any of the RCTs and observational

studies published later. The standard care and support given to participants in the early studies may be different from what a patient receives today, lowering the generalizability of the results to current Canadian settings. Patients who were pregnant or lactating were excluded from participating in included studies, further lowering the generalizability of the results. Three of the included RCTs[19,21,22] were terminated early and before recruiting the planned number of participants; two of the RCTs may have lacked adequate statistical power to detect significant differences between the groups.[19,22] Results from the included RCTs were from a follow-up period of 28 days or less. No evidence was found regarding the effectiveness and safety of corticosteroid therapy in the long term among patients with COVID-19. No evidence was found comparing the effectiveness of systemic corticosteroid therapy to other active treatments (e.g., remdesivir).

Conclusions and Implications for Decision or Policy-Making

Five SRs[14-18] and four RCTs[19-22] were identified regarding the clinical effectiveness of systemic corticosteroids for the treatment of COVID-19.

Findings were inconsistent for mortality; compared to no corticosteroids or standard care, corticosteroids were associated with significantly less,[16,20,21] greater,[15,18] or no significant difference[14,15,19,20,22] in mortality.

There was no difference between treatment with steroids versus standard care or placebo for sequential organ failure assessment,[21] pulmonary fibrosis,[20] bronchiolitis obliterans with organizing pneumonia,[20] or lung inflammation absorption time.[14] A decrease in duration of fever was found with corticosteroids versus non-corticosteroid comparator in one SR.[14]

Contrasting findings suggesting prolonged-[16] or no difference[20] in viral shedding or presence of viral RNA detection in patients treated with corticosteroids compared to non-corticosteroid treatment in one included study in the SR by Veronese et al., [16] and placebo in one RCT.[20]

Steroid treatment was associated with higher ICU admissions among patients with COVID-19 and pneumonia in one observational study included in one SR.[16] Two meta-analyses[14,15] showed longer duration- or no difference in duration of hospital stay between steroid and non-steroid comparators, while three RCTs[20-22] showed no difference between corticosteroid intervention and comparator (placebo)[20] or non-corticosteroid treatment[21,22] for duration of hospitalization or ICU-free days.

Adverse events were assessed in two of the five SRs, and neither SR reported any adverse events.[14,17] In the three RCTs that assessed adverse events, there were no significant differences between corticosteroid and non-corticosteroid comparator groups.[19,21,22]

The body of evidence included in this review consisted largely of research conducted early in the pandemic, with little follow-up (up to a maximum of 28 days). Therefore, the standard of care employed in the comparator groups is likely to differ from the care that is currently provided, and it is unknown whether any delayed-onset or enduring adverse events occurred.

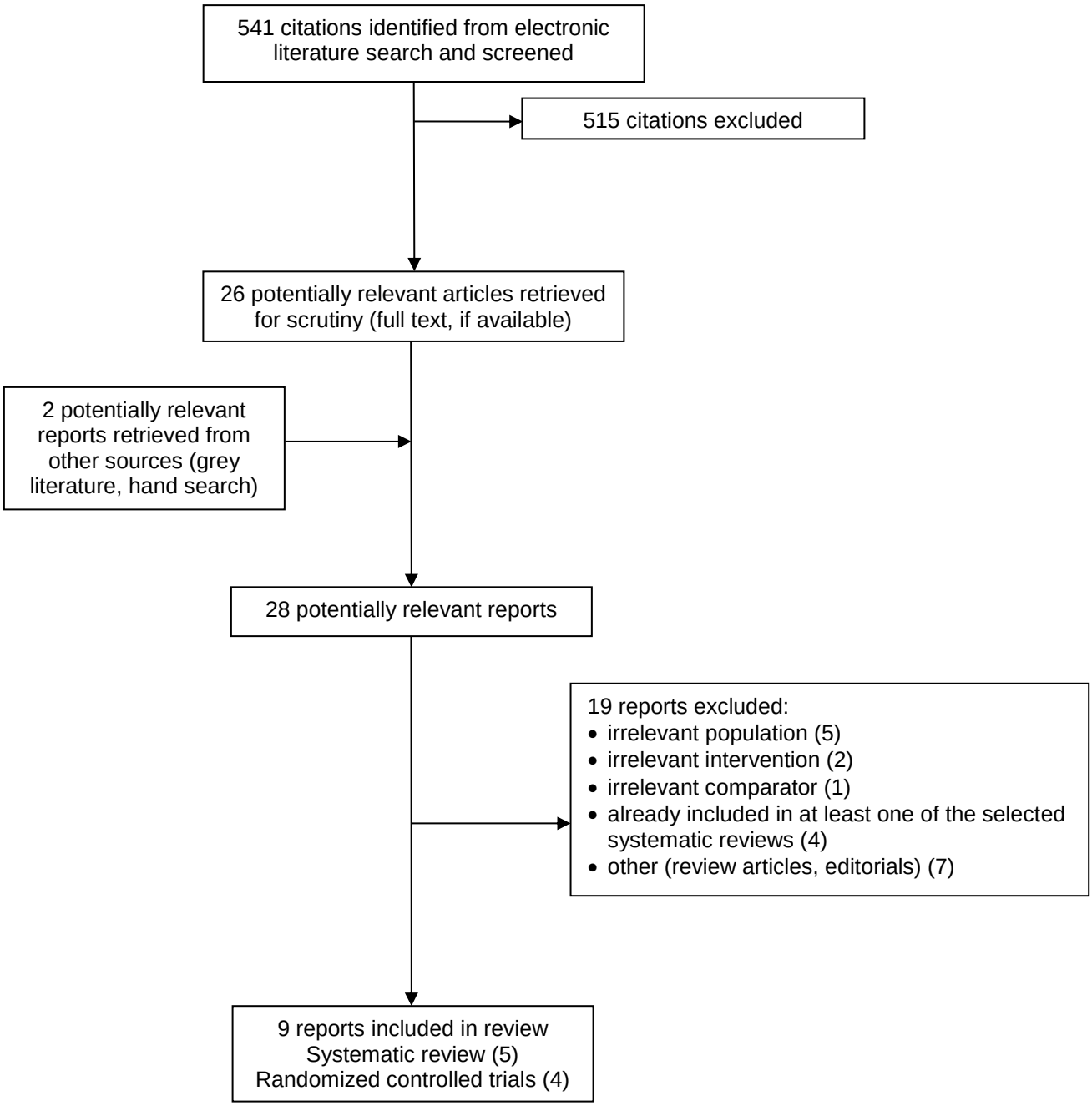
Further research addressing the effectiveness of systemic corticosteroids using well-designed RCTs with adequate sample sizes, longer duration of follow-up, and comparisons with other active drugs are needed to reduce uncertainty. Canada currently advises treatment with dexamethasone 6 mg intravenously for ten days or discharge (whichever is

earlier), or an equivalent glucocorticoid dose for patients who require supplemental oxygen or mechanical ventilation.[1] This advice is based on preliminary data from the RECOVERY trial (captured in the SR by Sarkar et al.[15]), which showed benefit in mortality at twenty-eight days for patients who required respiratory support at randomization and no benefit for those who did not.[10] Research that examines sub-groups of patients with COVID-19 and different stages of disease progression will provide clarity around existing guidance for the management of COVID-19 offered by the Public Health Agency of Canada and other jurisdictions.

References

1. Public Health Agency of Canada. Clinical management of patients with COVID-19: second interim guidance. 2020; https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html#a1. Accessed 2020 Oct 8.
2. Gorbalenya AE, Baker SC, Baric RS, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5(4):536-544.
3. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 2020 Oct 8.
4. World Health Organization. WHO Coronavirus disease (COVID-19) dashboard 2020; https://covid19.who.int/. Accessed 2020 Oct 5.
5. Public Health Agency of Canada. Coronavirus disease (COVID-19): outbreak update. 2020; https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection.html. Accessed 2020 Oct 8.
6. Ge H, Wang X, Yuan X, et al. The epidemiology and clinical information about COVID-19. *Eur J Clin Microbiol Infect Dis.* 2020;39(6):1011-1019.
7. World Health Organization. Clinical management of COVID-19 Interim guidance:WHO/2019-nCoV/clinical/2020.5. 2020: https://www.who.int/publications/i/item/clinical-management-of-covid-19. Accessed 2020 Oct 8.
8. Idda ML, Soru D, Floris M. Overview of the first 6 months of clinical trials for COVID-19 pharmacotherapy: the most studied drugs. *Front Public Health.* 2020;8:497-497.
9. Ali MJ, Hanif M, Haider MA, et al. Treatment options for COVID-19: a review. *Front Med (Lausanne).* 2020;7:480.
10. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med.* 2020;17:17.
11. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
12. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
13. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA.* 2020;02:02.
14. Lu S, Zhou Q, Huang L, et al. Effectiveness and safety of glucocorticoids to treat COVID-19: a rapid review and meta-analysis. *Ann Transl Med.* 2020;8(10):627.
15. Sarkar S, Khanna P, Soni KD. Are the steroids a blanket solution for COVID-19? A systematic review and meta-analysis. *J Med Virol.* 2020;03:03.
16. Veronese N, Demurtas J, Yang L, et al. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. *Front Med (Lausanne).* 2020;7:170.
17. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect.* 2020;81(1):e13-e20.
18. Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ.* 2020;192(27):E756-E767.
19. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA.* 2020;324(13):1298–1306.
20. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase iib, placebo-controlled trial. *Clin Infect Dis.* 2020;12:12.
21. f BM, Maia IS, Cavalcanti AB, 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 randomized clinical trial. *JAMA.* 2020;02:02.
22. Writing Committee for the Remap- C. A. P. Investigators, Angus DC, Derde L, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA.* 2020;02:02.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country, Funding sources	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Lu et al., 2020[14] **China** **Funding Source:** • National Clinical Research Center for Child Health and Disorders (Children's Hospital of Chongqing Medical University, Chongqing, China) (grant number NCRCCHD-2020-EP-01). • Special Fund for Key Research and Development Projects in Gansu Province in 2020. • The fourth batch of "Special Project of Science and Technology for Emergency Response to COVID-19" of Chongqing Science and Technology Bureau. • Special funding for prevention and control of emergency of COVID-19 from Key Laboratory of Evidence Based Medicine and Knowledge Translation of Gansu Province (grant number No. GSEBMKT-2020YJ01). • The Fundamental Research Funds for the Central Universities (lzujbky-2020-sp14).	**Study designs:** RCTs and cohort studies **Number of primary studies included:** 23 **Number of relevant primary studies included:** 5	**Relevant population:** Patients diagnosed with COVID-19 irrespective of the diagnostic criteria. **Number of patients in relevant analytical sample**: 926 **Mean age of relevant analytical sample**: Ranged from 48.7 years (SD = 18.6) to 56.3 years (SD = 15.7) in primary studies **Sex of relevant analytical sample:** 44.8% females	**Intervention**: Combination of glucocorticoids and symptomatic treatment **Comparator**: Symptomatic treatment alone	**Outcomes**: **Primary outcome:** Mortality **Secondary outcomes:** Duration of lung inflammation absorption, duration of hospital stay, duration of fever, adverse events (e.g., coinfections, kaliopenia, hypokalemia, osteonecrosis of femoral head). **Follow-up**: Follow-up duration not reported

First Author, Publication Year, Country, Funding sources	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Sarkar et al., 2020[15] India **Funding Source:** Non-funded	**Study designs:** RCTs and cohort studies **Number of primary studies included:** 15 **Number of relevant primary studies included:** 15 **Number of relevant primary studies included in MA:** 12	Patients with COVID-19 **Number of patients in relevant analytical sample:** 15, 754 **Mean age of relevant analytical sample:** Not reported **Sex of relevant analytical sample:** Not reported	**Intervention:** Systemic steroids: Methylprednisone; Dexamethasone; Hydrocortisone; Or not specified **Comparator:** no steroid	**Outcomes:** **Primary outcome:** Mortality **Secondary outcomes:** Duration of hospital stay, duration of viral shedding **Follow-up:** Follow-up duration not reported
Veronese et al., 2020[16] **Italy** **Funding Source:** Not reported	**Study designs:** Randomized and observational studies **Number of primary studies included:** Four **Number of relevant primary studies included:** Four	Patients with a validated diagnosis of COVID-19 irrespective of stage or severity. **Number of patients in relevant analytical sample:** 542 **Mean age of relevant analytical sample:** 52 years (range 34 to 68) **Sex of relevant analytical sample:** 55.7% males	**Intervention:** Corticosteroids irrespective of dosage and route of administration. **Comparator:** no steroid	**Outcomes:** All health outcomes **Follow-up:** Follow-up duration not reported
Yang et al., 2020[17] **China** **Funding Source:** National Natural Science Foundation of China (Jing Liu, grant no. 81472735) and the Wuhan University (Jing Liu, grant no. 2042019kf0206).	**Study designs:** Retrospective observational studies. **Number of primary studies included:** 15 **Number of relevant primary studies included:** None	Adult patients with coronavirus infection. **Number of patients in relevant analytical sample:** 179 **Mean age of relevant analytical sample**: Not reported **Sex of relevant analytical sample:** Not reported	**Intervention:** Corticosteroid therapy **Comparator:** No steroid	**Outcomes:** Mortality, length of stay, adverse reactions to corticosteroids **Follow-up:** Follow-up duration not reported

First Author, Publication Year, Country, Funding sources	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Ye et al., 2020[18] **Canada** **Funding Source:** None	**Study designs:** RCTs, retrospective cohort studies & case control studies **Number of primary studies included:** 35 **Number of relevant primary studies included:** 6 retrospective cohort studies (1 COVID-19 and ARDS; 5 COVID-19 mixed severity)	Patients with COVID-19 **Number of patients in relevant analytical sample:** 763 **Mean age of relevant analytical sample**: Not reported **Sex of relevant analytical sample:** Not reported	**Intervention:** steroid (methyl prednisone or not reported) **Comparator:** no steroid	**Outcomes:** mortality, ICU admission, duration of viral shedding **Follow-up:** Follow-up duration not reported

ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; RCT = randomized controlled trial; SD = standard deviation.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trial				
Dequin et al., 2020[19] **Trial name:** CAPE-COVID trial France **Funding Source:** French Ministry of Health, Programme Hospitalier de Recherche Clinique (PHRC) (2014 [CAPE-COVID parent trial], 2020 [CAPE-COVID subtrial]).	**Study design:** Multicenter randomized double-blind sequential trial	**Population:** Adult (≥ 18 years of age) patients with biologically confirmed (RT-PCR) or suspected (suggestive CT chest findings) COVID-19 and admitted to ICU. One of four of the severity criteria needed to be met: (i) mechanical ventilation with a PEEP of 5cm H_2O or more (ii) ratio of PaO_2 : FiO_2 < 300 on high-flow O_2 therapy, with an FiO_2 of ≥ 50% (iii) for patients receiving supplemental O_2, a PaO_2 : FiO_2 ratio < 200 (estimated using prespecified charts) (iii) pulmonary severity index > 130 **Exclusion criteria:** Septic shock (treated by vasopressors); pneumonia due to aspiration; history of cystic fibrosis, post-obstructive pneumonia, PCR positive influenza, active infections	**Intervention:** Intravenous hydrocortisone Initial dose of 200 mg / day (continuous infusion) Then 200 mg / day for first 7 days, then 100 mg / day for 4 days, 50 mg / day for 3 days (Total 14 days) Shorter treatment regimen if the patient's respiratory and general status was improved by day 4: 200 mg / day for first 4 days, 100 mg/day for 2 days and 50 mg / day for next two days (Total 8 days) Eligibility criteria for short regime:	**Primary outcome:** Treatment failure on day 21 (death or continued dependency on mechanical ventilation/ high-flow O_2 therapy) **Secondary outcomes:** Proportion of patients needing tracheal intubation, use of prone position, ECMO or nitric oxide inhalation**,** PaO_2:FiO_2 on days 1-7, then day 14 and day 21; proportion of patients with nosocomial infections, adverse events

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		(e.g., tuberculosis, fungal infection, viral hepatitis); need for corticosteroids for any reason; prednisone treatment (> 30 days) at baseline; pregnancy / lactation **Number of patients:** N = 143 Hydrocortisone group, n = 76 Placebo group, n = 73 **Median age (IQR), years:** Hydrocortisone group, 63.1 (51.5 to 70.8) Placebo group, 66.3 (53.5 to 72.7) **Sex (%):** Hydrocortisone group, 28.9% females Placebo group: 31.5% females	Spontaneous breathing; PaO_2:FiO_2 > 200, SOFA score on day 4 ≤ SOFA score on day 1; high chance of discharge from ICU before day 14. Treatment was stopped on ICU discharge for all patients. **Comparator:** Placebo (saline)	**Follow-up:** Day 28 for nosocomial infections. Day 21 for other outcomes.
Jeronimo et al., 2020[20] **Trial name:** Metcovid Brazil **Funding Source:** *Zona Franca de Manaus* (SUFRAMA), *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES), *Departamento de Ciência e Tecnologia/Ministério da Saúde* (DECIT), *Ministério da Ciência, Tecnologia e Inovações* (MCTI), *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, grant 403253/2020-9), *Fundação de Amparo à Pesquisa*	**Study design:** Parallel, double-blinded Phase IIb clinical trial	**Population:** Adult (≥18 years of age) patients with a clinical and/or radiological suspicion of COVID-19, SpO_2 ≤94% in room air or supplementary oxygen or under mechanical ventilation. Clinical and or radiological criteria included • History of fever and any respiratory symptoms (cough, dyspnea) and/or • Ground glass opacity or pulmonary consolidation on CT scan **Exclusion criteria:** hypersensitivity to MP, HIV / AIDS, chronic use of corticosteroids or immunosuppressive agents, pregnancy or lactation, decompensated cirrhosis, or chronic renal failure. **Number of patients:** N = 393 MP group, n = 194 Placebo group, n = 199 **Mean age (SD), years:** MP group: 54 (15)	**Intervention:** sodium succinate methyl prednisolone 0.5 mg / kg twice daily for five days. **Comparator:** Placebo (saline solution) All patients meeting ARDS criteria were administered IV ceftriaxone, 1 g twice daily for 7 days, and azithromycin (500 mg once daily for 5 days) or clarithromycin (500 mg twice daily for 7 days) from day 1.	**Primary outcome:** 28-day mortality **Secondary outcomes:** • Mortality at day 7 and day 14 • Need for orotracheal intubation by day 7 • Proportion of patients with PaO_2 / FiO_2 <100 by day 7. **Follow-up:** 28 days

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
do Estado do Amazonas (FAPEAM) (PAPAC 005/2019 and Pró-Estado public calls), and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (2020/05369-6).		Placebo group: 54 (15) **Sex (%):** MP group: 35.1% females Placebo group: 35.7% females		
Tomazini et al., 2020[21] **Trial name:** CoDEX Brazil **Funding Source:** Coalition COVID-19 Brazil; Laboratorios Farmaceuticos	**Study design:** investigator initiated, multicenter, open-label, RCT	Adult patients with ARDS (diagnosed according to Berlin criteria) due to confirmed or probable COVID-19 admitted to ICU Follow up completed July 21, 2020 **Number of patients:** Trial was stopped early before reaching 350 planned participants N = 299 patients were randomized to intervention (n = 151) and comparator (n = 148) groups **Mean age (SD):** 61 (14) years **Sex (%):** 37% women 63% men	**Intervention:** intravenous dexamethasone 20 mg per day x 5 days; 10 mg per day until ICU discharge, plus standard care **Comparator:** Standard care	**Relevant outcomes:** 28-day survival Days free from ventilator during first 28 days for at least 48 consecutive hours **Secondary outcomes:** All-cause mortality at 28 days Clinical status of patients at day 15 - assessed by WHO 6-point ordinal scale (ranging from 1, not hospitalized to 6, death) ICU-free days during the first 28 days Mechanical ventilation duration at 28 days Organ failure • assessed by SOFA • scores (range, 0-24, higher scores indicate greater organ dysfunction) **Follow-up:** 28 days or until discharge (whichever came first)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
				SOFA assessed at 48 hours, 72 hours, 7 days
The Writing Committee for the REMAP-CAP Investigators, 2020[22] **Trial name:** REMAP-CAP **US** **Funding source:** 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 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	**Study design:** Randomized, multi-factorial study (evaluates several treatment options simultaneously), embedded in routine care, that uses an adaptive platform, i.e., the intervention(s) evolve over time (e.g., in the event of pandemics new interventions may be introduced; or as new information is learned from interim analysis, such as the randomization algorithm being modified to randomize proportionately more patients to an intervention arm that is shown to be effective)	Adult patients with presumed or confirmed SARS-CoV-2 infection who had severe illness and admitted to ICU. *Criteria for severe illness*: Admitted to ICU for respiratory or cardiovascular organ support. *Respiratory support*: invasive or non-invasive mechanical ventilation, or high-flow nasal cannula if the flow rate was ≥ 30L / min or FiO_2 ≥ 0.4. *Cardiovascular organ support*: intravenous infusion of any vasopressor or inotrope. **Exclusion criteria:** Presumption of imminent death and lack of commitment to full active treatment in the trial; previous participation in the broader study in the prior 90 days; Hypersensitivity to HC; Systemic corticosteroid use; More than 36 hours since ICU admission; Intention to prescribe corticosteroids for a reason unrelated to COVID-19 **Number of patients:** N = 403 Fixed-dose HC, n = 137 Shock-dependent HC, n =146 No HC group, n = 101 **Mean age (SD), years:** Fixed-dose HC = 60.4 (11.6) Shock-dependent HC = 59.5 (12.7) No HC group = 59.9 (14.6) **Sex (%):** Fixed-dose HC = 28.5% females	**Intervention:** 1) **Fixed dose:** Intravenous hydrocortisone-50 mg, every 6 hours for 7 days, OR 2) **Shock-dependent:** Intravenous hydrocortisone, 50 mg every six hours while in shock for up to 28 days **Comparator:** No hydrocortisone or other corticosteroids. In all groups corticosteroids were allowed for indications such as post-extubation stridor, bronchospasm or anaphylaxis**.**	**Primary outcome:** Respiratory and cardiovascular organ support-free days **Secondary outcomes:** In hospital mortality; Length of ICU stay; Length of hospital stay; Cardiovascular organ support-free days; Progression to invasive mechanical ventilation; ECMO or death among those not ventilated at baseline; Disease status at day 14 based on WHO ordinal scale (range 0=8, where 0 is no illness and 8 is death) **Follow-up:** 21 days

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Program, the Breast Cancer Research Foundation, the French Ministry of Health (grant PHRC-20-0147), and the Minderoo Foundation.		Shock-dependent HC = 29.5% females No HC group = 28.7% females		

ARDS = acute respiratory distress syndrome; -19 = coronavirus disease 2019; CT = computerized tomography; ECEMO = Extracorporeal membrane oxygenation; FiO2 = fraction of inspired oxygen; H2O = water; HC = hydrocortisone; ICU = intensive care unit; IQR = interquartile ratio; IV = intravenous; mg = milligrams; MP = methylprednisolone; N = sample size; n = subsample size; O2 = oxygen; PaO2 = partial pressure of oxygen; PCR = polymerase chain reaction; PEEP = Positive End-Expiratory Pressure; RCT = randomized controlled trial; RT-PCR = reverse transcriptase polymerase chain reaction; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome-corona virus disease-2; SD = standard deviation; SOFA = Sequential Organ Failure Assessment; SpO2 = oxygen saturation.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[11]

Strengths	Limitations
Lu et al., 2020[14]	
• The objectives and inclusion criteria of the review were clearly reported and included components of population, intervention, comparators and outcome. • The authors conducted a comprehensive literature search involving multiple electronic databases. References of identified systematic reviews were searched for additional studies. A detailed search strategy was reported. Publication and language restrictions were reported and justified. • Study selection, data extraction and risk of bias assessment were conducted independently by two reviewers, lowering the risk of errors. • Characteristics of included studies were described in detail. • Valid tools were used to conduct risk of bias assessment of the included studies (Cochrane risk of bias for RCTs and Newcastle-Ottawa scale for cohort studies) and for the quality of evidence (GRADE). • A meta-analysis was performed using appropriate statistical techniques using random-effects model. Heterogeneity was assessed using I^2 statistic. • Predetermined subgroup analysis and sensitivity analysis was done. • Risk of bias assessments and heterogeneity were considered while interpreting evidence from meta-analyses. • Publication bias was assessed using Eggers test, which showed a bias was unlikely (P = 0.619). • The review authors had no significant conflicts of interest to declare.	• The review methods and protocol were not registered or published a priori. • Review authors did not explain their selection of the study designs for inclusion in the review. • Although the number of excluded studies were provided, reason for exclusion were not reported. • Non-peer-reviewed data from preprint publications were included in this study. • Definition of the outcome “duration of lung inflammation absorption” was unclear from the review. • The dosage and administration of corticosteroids in the relevant primary studies were not reported. • Sources of funding for the included primary studies were not reported. • It was unclear whether the sources of heterogeneity within the studies were investigated.
Sarkar et al., 2020[15]	
• The objectives and inclusion criteria of the review were clearly reported and included components of population, intervention, comparators and outcome. • The authors conducted a comprehensive literature search involving multiple electronic databases. A detailed search strategy was reported. Publication and language restrictions were reported and justified. • Study selection, data extraction and risk of bias assessment were conducted independently by two reviewers, lowering the risk of errors. • Characteristics of included studies were described in detail. • Valid tools were used to conduct risk of bias assessment of the included studies (Cochrane risk of bias for RCTs and ROBINS-I for cohort studies) and the quality of evidence (GRADE). • A meta-analysis was performed using appropriate statistical techniques. Heterogeneity was assessed using I^2 statistic.	• The review methods and protocol were not registered and published a priori. • Review authors did not explain their selection of the study designs for inclusion in the review. • Although the number of excluded studies were provided, a list of excluded studies with reasons for exclusion were not provided. • Non-peer-reviewed data from preprint publications were included in this study. • Demographic characteristics (e.g., mean age, sex) and length of follow up of study participants from the included primary studies were not reported. • Sources of funding for the included primary studies were not reported. • The overall meta-analysis and subgroup analyses of the outcomes mortality and duration of hospital stay had high heterogeneity lowering the validity of the results. The sources of heterogeneity were not discussed.

Strengths	Limitations
• Risk of bias assessments and heterogeneity were considered while interpreting evidence from meta-analyses. • Publication bias was assessed using a Funnel plot, which showed a bias was unlikely. • The review authors had no significant conflicts of interest to declare.	
Veronese et al., 2020[16]	
• The objectives and inclusion criteria of the review were clearly reported and included components of population, intervention, comparators and outcome. • The explanation for including randomized and non-randomized trials were reported. • The authors conducted a comprehensive literature search involving multiple electronic databases. Reference lists of identified studies were searched for additional studies. A detailed search strategy was reported. Handsearching of included studies and conference abstracts was done to identify additional studies. • Study selection and data extraction were conducted independently by two reviewers, lowering the risk for errors. • The number of excluded studies were provided and reasons for exclusion were reported. • The authors had no conflicts of interest to report.	• It was unclear whether the review methods and protocol were registered or published a priori. • Review authors did not explain their selection of the study designs for inclusion in the review. • The study designs of the included studies were unclear. • Quality assessment of the included studies was not done. Risk of bias from individual studies was not considered in the interpretation of results. • Publication bias was not assessed. • Funding sources of the systematic review and of the included studies were not reported.
Yang et al., 2020[17]	
• The objectives and inclusion criteria of the review were clearly reported and included components of population, intervention, comparators and outcome. • The authors conducted a comprehensive literature search involving multiple electronic databases. References lists of identified studies were searched for additional studies. A detailed search strategy was reported. Handsearching of included studies was done to identify additional studies. • Study selection and data extraction were conducted independently by two reviewers, lowering the risk for errors. • Risk of bias of the included studies were assessed using Newcastle-Ottawa scale, which is a valid tool. • Characteristics of include studies such as study design, population, intervention, other treatments and outcomes were described. • A meta-analysis was performed using appropriate statistical techniques. Heterogeneity was assessed using I^2 statistic. • Risk of bias assessment and heterogeneity were considered while interpreting evidence from meta-analyses. Subgroup analyses was conducted to examine the sources of heterogeneity. • Publication bias was assessed using funnel plots. (although some publication bias was identified for the outcome mortality, it was not relevant to the current report, as no eligible data were reported). • The study authors reported conflicts of interest (there were none).	• It was unclear whether the review methods and protocol were registered and published a priori. • Review authors did not explain their selection of the study designs for inclusion in the review. • Study results from individual studies were not reported in the review. • Although the number of excluded studies was provided, a list of excluded studies with reasons for exclusion was not provided. • Funding sources of the included studies were not reported.

Strengths	Limitations
Ye et al., 2020[18]	
• The objectives and inclusion criteria of the review were clearly reported and included components of population, intervention, comparators and outcome. • Review methods were established prior to the conduct of the review; however, authors did not report whether there were any deviations from the protocol. • The authors conducted a comprehensive literature search involving multiple electronic databases. References of identified studies were searched for additional studies. A detailed search strategy was reported. • Study selection, data extraction and risk of bias assessment were conducted independently by two reviewers, lowering the risk of errors. • Risk of bias in individual studies was assessed using the revised Newcastle-Ottawa scale. • Characteristics of included studies such as study design, population, intervention and outcomes were described. • Appropriate methods for statistical combination of results were used. • Review authors accounted for risk of bias in individual studies when interpreting the results of the review. • There was no significant heterogeneity.	• Review authors did not explain their selection of the study designs for inclusion in the review. • A list of potentially relevant studies that were read in full-text form but excluded from the review was not provided; exclusions for each study were not provided. • Study comparators were not described in adequate detail. • Review authors did not report the sources of funding for the studies included in the review. • Review authors reported a plan to investigate publication bias but it is not clear how or if this was done. • One author disclosed being an investigator on a trial evaluating the effect of corticosteroids in COVID-19 patients. However, the author did not explain how this potential important conflict of interest was resolved. • Non-peer-reviewed data from preprint publications were included in this study.

COVID-19 = coronavirus disease 2019; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; P = probability; RCT = randomized controlled trial; ROBINS-I = Risk Of Bias In Non-randomized Studies - of Interventions.

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black checklist[12]

Strengths	Limitations
Dequin et al., 2020[19]	
• The study was designed as a double-blinded randomized study with randomized allocation and concealment of allocation. • The objectives of the study were clearly described. The inclusion criteria, intervention, comparators and outcomes were clearly described. • Characteristics of patients were clearly described, including inclusion and exclusion criteria. • Study findings were clearly described in the form of simple outcome data. Appropriate statistical tests were conducted to compare the groups. Estimates of random variability were provided such as confidence intervals and interquartile ranges. Actual probability values were reported for all outcomes. • Patients lost to follow up and withdrawn from the study were accounted for. For the primary outcome, missing data were conservatively considered treatment failure. • Study participants were representative of the population from which they were enrolled. Study participants of both groups were enrolled from same population over the same period of time. The staff, places and facilities for this multicenter study	• The study was discontinued early as per the decision of the DSMB. The study did not enroll enough participants to ensure adequate power as per the reported sample size estimation. • The baseline characteristics of study participants in the treatment and control group were not statistically compared. Thus, it was unclear if the potential confounders were equally distributed between the groups. Adequate adjustment for confounders in the analysis was not done. • The study authors declared several conflicts of interests (e.g., related to involvement with pharmaceutical companies). It was unclear whether these conflicts were relevant to the study.

Strengths	Limitations
were representative of the care majority of patients would receive. • Participants in both groups were followed up for the same duration. • A sample size calculation was done and reported based on the primary outcome. • Serious adverse events in both groups were reported. There were three events in the treatment group and no events in the control group.	
Jeronimo et al., 2020[20]	
• The study was designed as a double-blinded randomized study with randomized allocation and concealment of allocation. • The objectives of the study were clearly described. The inclusion criteria, intervention, comparators and outcomes were clearly described. • Characteristics of patients were clearly described, including inclusion and exclusion criteria. • Study findings were clearly described in the form of simple outcome data. Appropriate statistical tests were conducted to compare the groups. Estimates of random variability were provided such as confidence intervals and interquartile ranges. Actual probability values were reported for all outcomes. • Patients lost to follow up and withdrawn from the study were accounted for. Modified intent-to-treat analysis and intent-to-treat analysis was conducted. • Study participants were representative of the population from which they were enrolled. The staff, places and facilities were representative of the care majority of patients would receive. • Participants in both groups were followed up for the same duration. • A sample size calculation was done and reported based on the primary outcome. The study enrolled enough participants to ensure adequate power. • The study authors described conflicts of interest (there were none).	• The baseline characteristics of study participants in the treatment and control group were not statistically compared. Thus, it was unclear if the potential confounders were equally distributed between the groups. Adequate adjustment for confounders in the analysis was not done. • Incidences of adverse events in treatment and control groups were not reported. • It is unknown if participants who were asked to participate in the study, or participants who prepared to participate in the study, were representative of the entire population from which they were recruited.
Tomazini et al., 2020[21]	
• The objectives of the study were clearly described. The inclusion criteria, intervention, comparators and outcomes were clearly described. • Characteristics of patients were clearly described, including inclusion and exclusion criteria. • Study findings were clearly described in the form of simple outcome data. Appropriate statistical tests were conducted to compare the groups. Estimates of random variability were provided, such as confidence intervals and interquartile ranges. Actual probability values were reported for all outcomes. • All important adverse events that may be a consequence of the intervention were measured and reported. • There were no losses to follow-up or missing data.	• Inclusion and exclusion criteria were changed after 182 participants had been enrolled; timing of ARDS diagnosis changed from 24 to 48 hours; pre-enrolment administration of corticosteroids for one day during hospital stay was allowed. Use of immunosuppressive drugs, cytotoxic chemotherapy in the past 21 days, and neutropenia due to hematological or solid malignancies with bone marrow invasion were added to the exclusion list. • It was not possible to blind investigators, health care providers, or participants to group allocation during the trial due to the nature of the intervention. • 23 invited participants refused consent. It is not known if they differed from included participants. • Validity and reliability of outcome measures were not reported by study authors.

Strengths	Limitations
• Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients received. • Results were not based on data dredging. • The study was stopped early due to evidence of benefit from another study. However, it was adequately powered for main study outcomes. • Distributions of principal confounders in each group of subjects to be compared were clearly described. A list of principal confounders was provided. • Patients in different intervention groups were recruited from the same population and over the same period of time. • The randomized intervention assignment was generated by the trial statistician who was not involved in patient care or enrolment. Randomization sequence was concealed from patients and health care staff until enrolment was finalized. • Intention-to-treat analysis was used. • Protocol deviations in the control group were reported (i.e., 35% of patients in the control received corticosteroids during the study period) and authors suggested this may have been related to the open-label design, disease severity, or other differences. However, authors reported this would have biased results toward the null whereas a benefit of the intervention on the primary outcome was identified.	• It is unknown if participants asked to participate in the study or participants prepared to participate in the study were representative of the entire population from which they were recruited.
The Writing Committee for the REMAP-CAP Investigators, 2020[22]	
• The objectives of the study were clearly described. The inclusion criteria, intervention, comparators and outcomes were clearly described. • Characteristics of patients were clearly described. • Study findings were clearly described in the form of simple outcome data. Appropriate statistical tests were conducted to compare the groups. The statistical analyses were done using Bayesian cumulative logistic model with a posterior distribution. Estimates of random variability was provided such as standard interval and interquartile ranges. • Any important adverse events that may be a consequence of the intervention were measured and reported. • The study enrolled participants from multiple study sites across countries, increasing the generalizability of the results. • Participants in both groups were followed up for the same duration.	• The baseline characteristics of study participants in the treatment and control group were not statistically compared. Thus, it was unclear if the potential confounders were equally distributed between the groups. Adequate adjustment for confounders in the analysis was not done. • Characteristics of patients lost to follow up were not described. It is possible they were different from those who continued in the study. • It is unknown if participants asked to participate in the study or participants prepared to participate in the study were representative of the entire population from which they were recruited. • The study was open label in design without blinding of participants or outcome assessors. • The trial was terminated early and did not enroll enough participants to ensure adequate power. • The reporting of study findings was challenging to interpret because of the way primary outcome was defined. • The analytical model assumed proportional effects across the primary outcome (ordinal organ support-free days). However, it was unclear whether this assumption was met. • Participants were permitted to participate in multiple intervention domains within the broader trial and the primary analysis of the study included all participants. The analysis of relevance to this report (i.e., the comparison of participants treated with corticosteroids and those without) did not account for co-interventions, and these may have been imbalanced between intervention and comparison groups.

Strengths	Limitations
	Thus, it was possible that the observed results were influenced by other interventions received by the patients. • Fifteen percent of the patients in the control group (no hydrocortisone group) received systemic hydrocortisone for other indications, increasing the likelihood of bias toward smaller effect sizes. • The study authors declared several conflicts of interests (e.g., involvement with pharmaceutical companies). It is unclear whether these conflicts were relevant to the study.

ARDS = acute respiratory distress syndrome; DSMB = Data and Safety Monitoring Board.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Lu et al., 2020[14]	
Systematic review and meta-analysis of five cohort studies to summarize the evidence for the effectiveness and safety of glucocorticoid therapy in COVID-19 patients. **Study findings** **Risk of mortality** Findings from five studies contributed to this analysis (n = 737) Number of deaths/ total number of patients: Steroid group: 94/329 Control group: 58/408 Steroid versus control, Risk Ratio (RR) (95% CI) = 2.00 (0.69 to 5.75) I^2 = 90.9%, P = 0.000 Quality of evidence: very low. **Duration of fever, days** Results from one study contributed to this analysis, (n = 46) Steroid group, mean (SD) = 2.06 (0.28) Control group, mean (SD) = 5.29 (0.7) Weighted mean difference (95% CI) = –3.23 (–3.56 to –2.90) Quality of evidence: very low. **Lung inflammation absorption time, days** Results from one study contributed to this analysis, (n = 72) Steroid group, mean (SD) = 13 (3.1) Control group, mean (SD) = 14 (4) Weighted mean difference (95% CI) = –1.00 (–2.91 to 0.91) Quality of evidence: very low. **Length of hospital stay, days** Results from two studies contributed to this analysis, (n = 365) Steroid group, mean (SD) = NR Control group, mean (SD) = NR Weighted mean difference (95% CI) = 2.43 (1.42 to 3.43) I^2 = 0.0%; P = 0.334 Quality of evidence: very low. Adverse events in steroid group: NR Adverse events in control group: NR	"In conclusion, glucocorticoid therapy may increase the risk of death in patients with coronavirus infections who have mild symptoms. We found no association between glucocorticoids and mortality in patients with severe symptoms. In the context of clinical trials, low-dose systemic glucocorticoid therapy for a short duration may be acceptable." (p. 18)[14]
Sarkar et al., 2020[15]	
Systematic review and meta-analysis to summarize the evidence regarding the efficacy and safety of systemic steroid therapy in patients with COVID-19. **Study findings:** **Mortality** Number of deaths/ total number of patients: Findings from 12 trials contributed to this analysis Corticosteroid: 1,306/5,611 No corticosteroid: 1,711/10,143	"In spite of some potential promising benefits, steroid therapy does not seem to reduce the risk of mortality, duration of hospital stays, and the period of viral shedding in COVID-19 patients. Further studies are necessary to substantiate the conclusive impact of steroids in COVID-19 patients." (p. 8)[15]

Main Study Findings	Authors' Conclusion
Steroid versus no steroid, OR (95% CI) = 1.94 (1.11 to 3.40) I^2 = 96%, P for heterogeneity <0.00001 *Increased mortality observed with steroid use* Quality of evidence: Low. **Duration of hospital stay, days** Findings from six trials contributed to this analysis Steroid versus no steroid, Mean Difference (95% CI) = 1.18 (–1.28 to 3.64) I^2 = 93%, P for heterogeneity <0.00001 Quality of evidence: Very low. **Period of viral shedding, days** Findings from two trials contributed to this analysis Steroid versus no steroid, Mean Difference (95% CI) = 1.42 (–0.52 to 3.37) I^2 = 0%, P for heterogeneity = 0.52 Quality of evidence: Low. **Subgroup analysis of mortality outcome:** **Mortality by Disease severity** Mild illness Steroid versus no steroid. OR (95% CI) = 1.21 (0.72 to 2.03) I^2 = 93%, P for heterogeneity = 0.0002 Critical illness Steroid versus no steroid. OR (95% CI) = 1.76 (0.85 to 3.65) I^2 = 95%, P for heterogeneity <0.00001 **Mortality by Dose of steroids** Low dose Steroid versus no steroid. OR (95% CI) = 2.23 (0.52 to 9.59) I^2 = 97%, P for heterogeneity <0.00001 Critical illness Steroid versus no steroid. OR (95% CI) = 0.67 (0.71 to 3.89) I^2 = 95%, P for heterogeneity <0.00001 Adverse events in steroid group: NR Adverse events in control group: NR	
Veronese et al., 2020[16]	
A systematic review to evaluate the effectiveness of glucocorticoid therapy in patients with COVID-19. **Findings from primary studies:** • **Liu et al., 2020** ◦ Number of participants, n = 137 ◦ Age, mean (SD) = 55 (16); Males, n = 61 ◦ Stage of COVID-19 = Pneumonia ◦ Participants receiving corticosteroids, % = 29.2 ◦ Findings: "Intravenous methylprednisolone (30–80 mg/day) did not show significant benefits. [No] numerical data were reported" (Table 2, p. 4)[16] • **Wang et al., 2020** ◦ Number of participants, n = 138 ◦ Age, mean/median (range) = 56 (42 to 68); Males, n = 75 ◦ Stage of COVID-19 = Pneumonia ◦ Participants receiving corticosteroids, % = 44.9	"In conclusion, the literature available so far does not fully encourage the routine use of corticosteroids in COVID-19, but some findings suggest that methylprednisolone could lower mortality rate in more severe forms of this condition, such as in ARDS. Findings from future clinical trials that are ongoing are needed to better understand the role of corticosteroids in COVID-19." (p. 5)[16]

Main Study Findings	Authors' Conclusion
○ Findings: "Glucocorticoid therapy was associated with a greater risk of ICU admission: 26 (72.2) vs. 36 (35.3), p < 0.001" (Table 2, p. 4)[16] • **Wu et al., 2020** ○ Number of participants, n = 201 ○ Age, mean/median (range) = 51 (43 to 60); Males, n = 128 ○ Stage of COVID-19 = Pneumonia ○ Participants receiving corticosteroids, % = 30.8 ○ Findings: "Administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20–0.72; P = 0.003) in subjects having ARDS for COVID 19." (Table 2, p. 4)[16] • **Ling et al., 2020** ○ Number of participants, n = 66 ○ Age, mean/median (range) = 44 (34 to 62); Males, n = 38 ○ Stage of COVID-19 = Convalescent ○ Participants receiving corticosteroids, % = 7.6 ○ Findings: "The duration of viral RNA detection for oropharyngeal swabs and feces in the corticosteroid treatment group was longer than that in the ○ Non-corticosteroid treatment group, which were 15 vs. 8.0 days (P = 0.013) and 20 vs. 11 days (P < 0.001)." (Table 2, p. 4)[16]	
Yang et al., 2020[17]	
A systematic review and meta-analysis of to identify the roles of corticosteroid treatment in adult patients with SARDS-CoV-2 infection**.** No relevant primary studies were included in the review.	"Patients with severe conditions were more likely to require corticosteroids. Corticosteroids could lead to higher mortality, longer LOS, a higher rate of bacterial infection and hypokalemia. Therefore, corticosteroid should be used with caution in the treatment of COVID-19 patients: corticosteroids are not recommended for patients with mild conditions, and moderate corticosteroids can be used in patients with severe conditions to suppress the immune response and reduce symptoms. Nevertheless, more multicenter clinical trials are needed to further verify this conclusion." (p. e19)[17]
Ye et al., 2020[18]	
Mortality Findings from 2 retrospective cohort studies on severe COVID-19 (n = 331) Corticosteroid vs. no corticosteroid HR (95% CI) = 2.30 (1.00 to 5.29) MD (95% CI) = 11.9 (0 to 33.7) (favours comparator group) I^2 = 0.0%, P = 0.768 Findings from 1 retrospective cohort study on COVID-19 and ARDS (n = 84) Methyl prednisone vs no steroid HR (95% CI) = 0.41 (0.20 to 0.83) MD (95% CI) = -29.2 (-44.3 to –6.8) (favours prednisone) **Mortality composite or ICU admission** Findings from 1 retrospective cohort study on mixed severity COVID-19 Steroid vs no steroid Increase in mortality composite outcome or ICU admission with steroid use vs. no steroid use	"Given the paucity of direct evidence and the limitations of indirect evidence, it is critical for clinicians and researchers to cooperate in conducting high-quality studies, in particular large and rigorous RCTs, to evaluate the effect of corticosteroids in both patients with COVID-19 and ARDS and patients with severe COVID-19 but who are not critically ill." (p. e765)[18]

Main Study Findings	Authors' Conclusion
(results not reported by review authors) **Viral shedding:** Findings from 2 retrospective cohort studies on mixed severity COVID-19 Steroid vs no steroid Prolonged viral shedding with steroid use vs. no steroid use (results not reported by review authors)	

ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus 2019; CI = confidence interval; HR = Hazard Ratio; ICU = intensive care unit; MD = mean difference; NR = not reported; OR = odds ratio; RNA = ribonucleic acid; RR = risk ratio; SD = standard deviation.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Dequin et al., 2020[19]	

CAPE-COVID Trial
 	
A double-blinded RCT to evaluate the efficacy of low-dose hydrocortisone compared to placebo in COVID-19 patients.
Total number of participants, N = 149
HC group, n = 76
Placebo group, n = 173
 	
Study findings:
• **Treatment failure on Day 21 (death or persistent dependence of mechanical ventilation or high-flow O2 therapy)**
  ○ HC group, n/N (%) = 32/76 (42.1)
  ○ Placebo group, n/N (%) = 37/73 (50.7)
  ○ Difference in proportions (95% CI) = –8.6 (–24.9 to 7.7); P = 0.29
 	
• **Nosocomial infections on day 28**
  ○ HC group, n/N (%) = 28/76 (37.7)
  ○ Placebo group, n/N (%) = 30/73 (41.1)
  ○ HR (95% CI) = 0.81 (0.49 to 1.35); P = 0.42
 	
• **Daily evolution of PaO2:FiO2 ratio**
  ○ "did not significantly differ between the groups" (p. E4)[19]
 	
Post-hoc outcomes
Status on day 21, n (%)
○ Death:
HC group = 11 (14.7); placebo group = 20 (27.4)
○ Difference in proportions (95% CI) = –12.7 (–25.7 to 0.3); P = 0.057
○ Mechanical ventilation:
HC group = 17 (22.7); placebo group = 17 (23.3)
○ High-flow O2 therapy:
HC group = 3 (4.0); placebo group = 0
○ Low flow O2 therapy:
HC group = 1 (1.3); placebo group = 4 (5.5)
○ Discharged from ICU:
HC group = 43 (57.3); placebo group = 32 (43.8)
○ Overall, the status "did not significantly differ between both groups (P = 0.06)" (supplement 3)[19]
 	
Serious adverse events:
• **Serious adverse events in** HC **group: n = 3**
	"In this study of critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone, compared with placebo did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. However, the study was stopped early and likely was underpowered to find a statistically and clinically important difference in the primary outcome." (p. E7)[19]

Main Study Findings	Authors' Conclusion
○ Cerebral vasculitis possibly related to SARS-CoV-2, n=1 ○ Cardiac arrest related to pulmonary embolism, n = 1 ○ Intraabdominal hemorrhage related to anticoagulant therapy for pulmonary embolism, n =1 ○ None were attributed to the study treatment. • **Serious adverse events in placebo group: n = 0**	
Jeronimo et al., 2020[20]	
Metcovid Trial A double-blinded RCT to evaluate the efficacy of methylprednisolone compared to placebo in COVID-19 patients. Total number of participants, N = 393 MP group, n = 194 Placebo group, n = 199 **Study findings:** • **28-day mortality:** ○ MP group, n/N (%) = 72/194 (37.1) ○ Placebo group, n/N (%) = 76/199 (38.2) ○ HR (95% CI) = 0.924 (0.669 to 1.275) ○ P = 0.629 • **7-day mortality:** ○ MP group, n/N (%) = 32/194 (16.5) ○ Placebo group, n/N (%) = 47/199 (23.6) ○ HR (95% CI) = 0.677 (0.432 to 1.061) ○ P = 0.089 • **14-day mortality:** ○ MP group, n/N (%) = 53/194 (27.3) ○ Placebo group, n/N (%) = 63/199 (31.7) ○ HR (95% CI) = 0.821 (0.570 to 1.183) ○ P = 0.290 • **Presence of viral RNA in the naso/oropharyngeal swab on day 5:** ○ MP group, n/N (%) = 69/144 (47.9) ○ Placebo group, n/N (%) = 66/139 (47.5) ○ HR (95% CI) = 0.43 (–11.1 to 11.9) ○ P = 0.942 • **Presence of viral RNA in the naso/oropharyngeal swab on day 7:** ○ MP group, n/N (%) = 61/117 (52.1) ○ Placebo group, n/N (%) = 50/95 (52.6) ○ HR (95% CI) = –0.49 (–13.7 to 12.8) ○ P = 0.943 • **Need for invasive mechanical ventilation until day 7**: ○ MP group, n/N (%) = 18/93 (19.4) ○ Placebo group, n/N (%) = 16/95 (16.8) ○ HR (95% CI) = 2.6 (–8.6 to 13.6) ○ P = 0.654 • **Proportion of patients with oxygenation index (PaO2/FiO2)<100 until day 7:** ○ MP group, n/N (%) = 21/60 (35.0) ○ Placebo group, n/N (%) = 13/51 (25.5) ○ HR (95% CI) = 9.51 (–7.70 to 25.59) ○ P = 0.279 • **Pulmonary fibrosis after day 7**: ○ MP group, n/N (%) = 12/34 (35.3)	"In conclusion, the use of MP during only 5 days in hospitalized patients with COVID-19 was not sufficient to improve prognosis, as opposed to RECOVERY trial, in which dexamethasone was successfully used for 10 days. Our exploratory analysis showed that MP reduces mortality in hospitalized patients older than 60 years with COVID-19. Caution is needed in the use of steroids in less severe patients, as a trend toward more harm was seen in the lower age group." (p. 16)[20]

Main Study Findings	Authors' Conclusion
○ Placebo group, n/N (%) = 3/22 (13.6) ○ HR (95% CI) = 21.7 (–2.4 to 40.7) ○ P = 0.074 • **Bronchiolitis Obliterans with Organizing Pneumonia after day 7:** ○ MP group, n/N (%) = 19/34 (55.9) ○ Placebo group, n/N (%) = 17/22 (77.3) ○ HR (95% CI) = –21.4 (–42.1 to 4.3) ○ P = 0.103 • **Length of hospitalization, days:** ○ MP group, median(IQR) = 10 (7 to 13) ○ Placebo group, median(IQR) = 9 (7 to 12) ○ P = 0.296 **Post-hoc analysis:** 28-day mortality among patients with age> 60 years ○ MP group, n/N (%) = 34/73 (46.6) ○ Placebo group, n/N (%) = 52/84 (61.9) ○ HR (95% CI) = 0.634 (0.411 to 0.978) ○ P = 0.039 Post-hoc analysis showed no significant differences in the outcome 28-day mortality between MP and placebo based on subgroup analyses based on invasive ventilation, non-invasive oxygen therapy, and laboratory results. Adverse events in steroid group: NR Adverse events in control group: NR	
Tomazini et al., 2020[21]	
CoDEX Dexamethasone (n = 151) vs. standard care (n = 148) **Study findings:** • **Days alive and ventilator free at 28 days** ○ Mean days (95% CI) = 6.6 (5.0 to 8.2) vs. 4.0 (2.9 to 5.4) ○ Adjusted MD (95% CI) = 2.26 (0.2 to 4.38); P = 0.04 ○ Unadjusted MD (95% CI) = 2.55 (0.46 to 4.6), P = 0.02 ○ (Favours dexamethasone) • **SOFA at day 15** ○ (Scores range from 0 to 24) ○ Median IQR (95% CI) = 5 (3 to 6) vs. 5 (5 to 6) ○ Adjusted OR (95% CI) = 0.66 (0.43 to 1.03); P = 0.07 ○ Unadjusted OR (95% CI) = 0.62 (0.41 to 1.15); P = 0.03 • **SOFA at 48 hours** ○ (Scores range from 0 to 24) ○ Mean (95% CI) = 8.1 (7.6 to 8.6) vs. 8.4 (7.8 to 8.9) ○ Adjusted MD (95% CI) = -0.11 (-0.86 to 0.63); P = 0.76 ○ Unadjusted MD (95% CI) = -0.24 (-1.0 to 0.51); P = 0.53 • **SOFA at 72 hours** ○ (Scores range from 0 to 24) ○ Mean (95% CI) = 7.7 (7.2 to 8.3) vs 8.3 (7.8 to 8.9) ○ Adjusted MD (95% CI) = -0.38 (-1.13 to 0.37); P = 0.32 ○ Unadjusted MD (95% CI) = -0.6 (-1.37 to 0.16); P = 0.12 • **SOFA at 7 days** ○ (Scores range from 0 to 24) ○ Mean (95% CI) = 6.1 (5.5 to 6.7) vs. 7.5 (6.9 to 8.1)	"In patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care, compared with standard care alone, resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days." (p. E8)[21]

Main Study Findings	Authors' Conclusion
○ Adjusted MD (95% CI) = -1.16 (-1.94 to -0.38); P = 0.004 ○ Unadjusted MD (95% CI) = -1.38 (-2.21 to -0.55); P = 0.001 • **All-cause mortality at 28 days** ○ 56.3% vs. 61.5% of patients ○ Adjusted HR (95% CI) = 0.97 (0.72 to 1.31); P = 0.85 ○ Unadjusted HR (95% CI) = 0.86 (0.64 to 1.15); P = 0.31 • **ICU-free days at 28 days** ○ Mean (95% CI) = 2.1 days (1.0 to 4.5) vs. 2.0 (0.8 to 4.2) ○ Adjusted MD (95% CI) = 0.28 (-0.49 to 1.02); P = 0.50 ○ Unadjusted MD (95% CI) = 0.14 (-0.92 to 1.27); P = 0.78 • **Mechanical ventilation duration (days)** ○ Mean (95% CI) = 12.5 (11.2 to 13.8) vs. 13.9 (12.7 to 15.1) ○ Adjusted MD (95% CI) = -1.54 (-3.24 to 0.12); P = 0.11 ○ Unadjusted MD (95% CI) = -1.46 (-3.10 to 0.57); P = 0.18 **Adverse Events** • **Serious adverse events** ○ n (%) = 5 (3.3) vs. 9 (6.1) ○ Absolute difference (95% CI) = 2.8 (-2.7 to 8.2) • **New diagnosis of infection until day 28** ○ n (%) = 33 (21.9) vs. 43 (29.1) ○ Absolute difference (95% CI) = 7.2 (-3.3 to 17.7) • **Ventilator-associated pneumonia** ○ n (%) = 19 (12.6) vs. 29 (19.6) ○ Absolute difference (95% CI) = 7.0 (-2.0 to 16.0) • **Catheter-related bloodstream infection** ○ n (%) = 10 (6.6) vs 8 (5.4) ○ Absolute difference (95% CI) = -1.2 (-7.3 to 4.8) • **Catheter-associated urinary tract infections** ○ n (%) = 1 (0.7) vs 0 (0) ○ Absolute difference (95% CI) = 0 • **Other** ○ n (%) = 6 (4) vs. 7 (4.7) ○ Absolute difference (95% CI) = 0.7 (-2.5 to 4.8) • **Bacteremia** ○ n (%) = 12 (7.9) vs. 14 (9.5) ○ Absolute difference (95% CI) = 1.5 (-5.5 to 8.6) • **Insulin use for hyperglycemia** ○ n (%) = 47 (31.1) vs. 42 (28.4) ○ Absolute difference (95% CI) = -2.7 (-13.8 to 8.3)	
The Writing Committee for the REMAP-CAP Investigators, 2020[22]	
REMAP-CAP trial A multicenter open-label RCT to evaluate the effect of intravenous hydrocortisone in patients with severe COVID-19. Total number of participants, N = 403 Fixed-dose HC, n = 137 Shock-dependent HC, n =146 No HC group, n = 101 **Study findings:** • **Organ support-free days:** ○ Fixed-dose HC, median (IQR) = 0 (–1 to 15) ○ Shock-dependent HC, median (IQR) = 0 (–1 to 13) ○ No HC, median (IQR) = 0 (–1 to 11)	"Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support–free days within 21 days. However, the trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions." (p. E11)[22]

Main Study Findings	Authors' Conclusion
○ **In hospital deaths:** ▪ Fixed-dose HC, n (%) = 41 (30) ▪ Shock-dependent HC, n (%) = 37 (26) ▪ No HC, n (%) = 33 (33) ○ **Organ support-free days among survivors** ▪ Fixed-dose HC, median (IQR) = 11.5 (0 to 17) ▪ Shock-dependent HC, median (IQR) = 9.5 (0 to 16) ▪ No HC, median (IQR) = 6(0 to 12) ○ **Adjusted odds ratio** ▪ Fixed-dose HC: Median (95 % CrI) = 1.45 (0.93 to 2.30) ▪ Shock-dependent HC: Median (95 % CrI) = 1.24 (0.80 to 1.95) ▪ No HC: Reference ○ **Probability of superiority to No HC:** ▪ Fixed-dose HC = 95%; Shock-dependent HC = 83% • **Time to death:** ○ **Adjusted hazard ratio:** ▪ Fixed-dose HC: Median (95 % CrI) = 0.94 (0.61 to 1.46) ▪ Shock-dependent HC: Median (95 % CrI) = 0.98 (0.63 to 1.54) ▪ No HC: Reference ○ **Probability of superiority to No HC:** ▪ Fixed-dose HC = 40%; Shock-dependent HC = 47% • **Respiratory support-free days:** ○ **Adjusted hazard ratio:** ▪ Fixed-dose HC: Median (95 % CrI) = 1.42(0.90 to 2.24) ▪ Shock-dependent HC: Median (95 % CrI) = 1.28 (0.81 to 2.00) ▪ No HC: Reference ○ **Probability of superiority to No HC:** ▪ Fixed-dose HC = 94%; Shock-dependent HC = 85% • **Cardiovascular support-free days**: ○ **Adjusted hazard ratio:** ▪ Fixed-dose HC: Median (95 % CrI) = 1.63(1.03 to 2.59) ▪ Shock-dependent HC: Median (95 % CrI) = 1.29 (0.81 to 2.00) ▪ No HC: Reference ○ **Probability of superiority to No HC:** ▪ Fixed-dose HC = 98%; Shock-dependent HC = 86% • **Length of ICU stay:** ○ **Adjusted hazard ratio:** ▪ Fixed-dose HC: Median (95 % CrI) = 0.92(0.68 to 1.24) ▪ Shock-dependent HC: Median (95 % CrI) = 0.85 (0.62 to 1.15) ▪ No HC: Reference ○ **Probability of superiority to No HC:** ▪ Fixed-dose HC = 29%; Shock-dependent HC = 14% • **Length of hospital stay:** ○ **Adjusted hazard ratio:** ▪ Fixed-dose HC: Median (95 % CrI) = 0.97(0.72 to 1.32) ▪ Shock-dependent HC: Median (95 % CrI) = 0.93(0.69 to 1.26) ▪ No HC: Reference ○ **Probability of superiority to No HC:** ▪ Fixed-dose HC = 43%; Shock-dependent HC = 31% • **Disease severity (measured using WHO scale) at day 14:** ○ **Adjusted hazard ratio:** ▪ Fixed-dose HC: Median (95 % CrI) = 1.29(0.83 to 2.05) ▪ Shock-dependent HC: Median (95 % CrI) = 1.03(0.65 to 1.65) ▪ No HC: Reference	

Main Study Findings	Authors' Conclusion
○ **Probability of superiority to No HC:** ▪ Fixed-dose HC = 87%; Shock-dependent HC = 55% • **Serious adverse events:** ○ Fixed-dose HC group, n (%) = 4 (0.03) ○ Shock-dependent HC group, n (%) = 5 (0.04) ○ No HC group, n (%) = 1 (0.01)	

CI = confidence interval; COVID-19 = coronavirus disease 2019; CrI = credible interval; FiO2 = fraction of inspired oxygen; HC = hydrocortisone; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; MD = mean difference; MP = methyl prednisolone; NR = not reported; OR = odds ratio; PaO2 = partial pressure of oxygen; RCT = randomized controlled trial; RNA = ribonucleic acid; SARS-CoV-2 = Severe Acute Respiratory Syndrome-related Coronavirus 2; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.

Appendix 5: Overlap Between Included Systematic Reviews

Table 8: Primary Study Overlap Between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation				
	Lu et al., 2020[14]	Sarkar et al., 2020[15]	Veronese et al., 2020[16]	Yang et al., 2020[17]	Ye et al., 2020[18]
Albani F,et al.,medRxiv. 2020.		x			
Corral L, et al., medRxiv. 2020.		x			
Fadel R, et al., Clin Infect Dis. 2020.		x			
Fang X, et al., J Infect. 2020; 81(1):147-178.		x			
Heili-Frades S, et al., medRxiv. 2020.		x			
Horby P, et al., N Engl J Med. 2020.		x			
Li Q, et al.,Infect Dis. 2020.		x			
Li. X. et al., Allergy Clin Immunol 2020; Apr. 12					x
Liang M,et al., Infect Dis. 2020.		x			
Ling Y, et al., Chin Med J. (2020).			x		
Liu K, et al., Chin Med J. (2020).			x		
Lu, X., et al., Crit Care. 2020; 24, 241		x			x
Majmundar M, et al., medRxiv. 2020.		x			
Ni Q, et al., Chin J Clin Infect Dis 2020;13.	x				
Salton F, et al., medRxiv. 2020.		x			
Shang J, et al., Pulmonology. 2020.	x	x			
Wang D et al., medRxiv 2020 Apr. 24.	x				x
Wang D, et al., JAMA. (2020) 323:1061–9.			x		
Wu. C et al., JAMA Intern Med. 2020; 180(7): 934 -943	x		x		x
Wu J, et al.,medRxiv. 2020.		x			
Xu K et al., Clin Infect Dis 2020; Apr. 9					x
Yan D et al., medRxiv 2020; Mar. 30.					x
Yuan M. et al., Shock. 2020.		x			
Zha L, et al.,Med J Aust. 2020;212: 416-420.		x			
Zhou F, et al., Lancet 2020;395:1054-62.	x				

Appendix 6: Additional References of Potential Interest

Guideline

Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for COVID-19. *BMJ*. 2020 09 04;370:m3379.
PubMed: PM32887691

Non-randomized Studies

Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, et al. A retrospective controlled cohort study of the impact of glucocorticoid treatment in SARS-CoV-2 infection mortality. *Antimicrob Agents Chemother*. 2020 08 20;64(9):20.
PubMed: PM32571831

Ma Y, Zeng H, Zhan Z, et al. Corticosteroid use in the treatment of COVID-19: a multicenter retrospective study in Hunan, China. *Front Pharmacol*. 2020;11:1198.
PubMed: PM32903363

Meta-Analysis Without Systematic Review

Wang Y, Ao G, Qi X, Zeng J. The influence of corticosteroid on patients with COVID-19 infection: a meta-analysis. *Am J Emerg Med*. 2020 Jun 23
PubMed: PM32616373

Alternative Intervention – Inhaled Corticosteroids

Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. *Eur Respir J*. 2020 05;55(5):05.
PubMed: PM32341100