Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Should intravenous corticosteroids be used in COVID-19?

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RECOMMENDATIONS

We recommend the use of dexamethasone for up to 10 days among patients with severe and critical COVID-19. *(Moderate certainty of evidence; Strong recommendation)*

We recommend the use of 6 mg to 12 mg per day of dexamethasone among patients with severe and critical COVID-19. *(Moderate certainty of evidence; Strong recommendation)*

We recommend against the use of corticosteroids among mild and moderate (non-oxygen requiring) COVID-19 patients. *(Moderate certainty of evidence; Strong recommendation)*

We suggest that steroid therapy be initiated as soon as diagnosed or categorized as severe and critical COVID-19. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues
The available data reviewed is still inconclusive to recommend high dose steroids for severe and critical COVID-19 patients. However, higher doses may still be considered since marginal benefit was found on ventilator-free days, cardiovascular-support free days, and renal replacement therapy-free days. Ideally, intravenous steroids are started for hospitalized patients but may be shifted to oral if deemed necessary or once able.

PREVIOUS RECOMMENDATION

We recommend the use of dexamethasone in patients with COVID-19 infection who require supplemental oxygenation (i.e., including high-flow device, non-invasive, invasive mechanical ventilation and ECMO). *(Moderate quality of evidence; Strong recommendation)*

We recommend against the use of systemic corticosteroids in patients with COVID-19 infection but not requiring oxygen supplementation. *(Moderate quality of evidence; Strong recommendation)*

Consensus Issues
Dexamethasone has a better pharmacokinetic profile (i.e., longer acting than hydrocortisone and methylprednisolone) and better anti-inflammatory effect as compared to other steroids with less corticoid effects (e.g., less water retention). Low-dose steroids (i.e., 6 mg of dexamethasone) are more preferred by physicians. As for other corticosteroids such as methylprednisolone and hydrocortisone, there is insufficient evidence to recommend its use in patients with COVID-19 infection who are requiring supplemental oxygenation.

What's new in this version?

- This review update focused on the use of different corticosteroids on severe and critical COVID-19. Three new randomized controlled trials, which provided data on the use of methylprednisolone versus placebo, were added in this review.
- One randomized controlled trial comparing 12mg and 6mg dexamethasone showed no significant difference in all-cause mortality (RR 0.85, 95% CI 0.72-1.01; moderate certainty), life support-free days (MD 2.80 days, 95% CI -0.20-5.8; moderate certainty) and development of any adverse event (RR 0.84, 95% CI 0.60-1.18; moderate certainty).
- Seven cohort studies on the timing of administration of corticosteroids showed significant benefit when systemic corticosteroids were started early within 24 hours of diagnosis or categorization of severe to critical COVID-19 compared to non-early initiation beyond 24 hours (OR 0.68, 95% CI 0.51-0.92; I^2=0%; low certainty).

Key Findings

Fourteen randomized controlled trials (RCTs) provided data on the effect of different intravenous (IV) corticosteroids versus placebo or standard of care on all-cause mortality in severe and critical COVID-19 patients. Compared to placebo, only dexamethasone showed a statistically significant reduction in the risk of mortality. However, patients in this group had significantly longer duration of hospital stay. In terms of adverse events, no significant difference was found between the IV corticosteroids and control groups. No significant benefit on 28-day mortality and a tendency towards harm were observed when dexamethasone was given to COVID-19 patients who did not require oxygen therapy.

In comparing 12 mg and 6 mg dosing of dexamethasone, no significant differences were found in terms of all-cause mortality and life support-free days while marginal benefits in ventilator-free days, cardiovascular support-free days, and renal replacement therapy-free days were observed in the 12 mg group. No significant difference in adverse events were observed between the two dosing regimens.

Seven retrospective cohort studies evaluated the effect in the timing of administration of different corticosteroids among severe and critical COVID-19 patients. Significant benefit was found only when systemic corticosteroids were started early within 24 hours of admission compared to non-early initiation beyond 24 hours. Mechanical ventilation was likewise significantly reduced when systemic corticosteroids were initiated within 24 hours of admission.

Introduction

The SARS-CoV-2 virus, the causative agent of COVID-19, is a highly transmissible and virulent organism responsible for the current global pandemic. Patients diagnosed with COVID-19, especially those ≥ 65 years old, who are smokers, and/or have comorbidities, are at risk for rapid deterioration and eventual need for hospital admission. This can be attributed to the body's inflammatory response which can release an excess of cytokines and inflammatory markers leading to organ damage such as acute respiratory distress syndrome (ARDS). Intravenous corticosteroids, a staple medication in the critical care setting, has been proven to have potent anti-inflammatory effects and has been used to treat other severe viral infections (e.g., SARS, MERS).[1] As it is a relatively affordable drug, it is readily accessible even in low-income countries.[2] However, because of its serious side effects, such as immunosuppression, hyperglycemia, and fungal infection, due caution must be given when deciding to give this treatment. As hospitals and ICUs continue to admit COVID-19 cases, healthcare providers must further investigate the potential effects of IV corticosteroids on these patients.[1,3]. This review aims to evaluate the effectiveness and safety of intravenous corticosteroids in COVID-19 patients.

Review Methods

We searched Cochrane Library, PubMed, MEDLINE, Google Scholar, JSTOR, HERDIN, WHO ICTRP and ClinicalTrials.gov using a combined MeSH and free text search with the terms "SARS-CoV-2", "COVID-19", "severe", "critical", "intravenous", "IV", "systemic", "dexamethasone", "hydrocortisone", "methylprednisolone", "high dose", "low dose", "mortality", "hospital length of stay", "ICU length of stay", "mechanical ventilation", "organ support-free days" OR "adverse events", "infection", "superinfection", "hyperglycemia", and "gastrointestinal bleeding". The study characteristics that were searched for were: Population – patients with severe or critical COVID-19; Intervention – IV corticosteroids; Comparator – standard care or placebo; Outcomes – mortality, length of hospital stay, length of ICU stay, organ support-free days, adverse events. Studies which recruited patients with moderately severe COVID-19 were included if the population was mixed with severely or critically ill patients. Randomized controlled trials were prioritized in the search; when none were found, non-randomized and observational studies were screened as well. When systematic reviews or meta-analyses were found, the individual studies were assessed for possible inclusion.

Results

We found 16 RCTs which used different IV corticosteroids as treatment for COVID-19. A total of 3,004 COVID-19 patients with severe and critical illness were analyzed in this review.[4-19] The included studies either compared IV corticosteroid use with standard of care or placebo [4-17], compared two different IV corticosteroids [18], or compared different doses of the same IV corticosteroid.[19] The IV corticosteroids used were dexamethasone (4 RCTs)[5,7,11,13], hydrocortisone (3 RCTs)[4,6,14], methylprednisolone (8 RCTs)[7,8,10,12,15,16], and prednisolone (1 RCT).[9] Duration of use for each of the IV corticosteroids were reported (Range; Mean ± SD) as follows: DEX (10 days), HCT (7-14 days; 9.33 ± 3.3 days), MP (3-10 days; 5.25 ± 2.28 days), and PRDL (5 days). Characteristics of included studies are summarized in Appendix 3.

Type of Corticosteroids

Fourteen RCTs provided data on all-cause mortality. Results showed that there was a significant decrease in all-cause mortality in the corticosteroid groups (RR 0.87, 95% CI 0.78-0.97; I^2=14%; moderate certainty).[4-16]

Dexamethasone

Compared to placebo, only DEX group showed statistically significant benefit in decreasing the risk of mortality (RR 0.86, 95% CI 0.79-0.94; I^2=0%; moderate certainty)[2,4,8,10] and benefit in ventilator-free days (MD 2.26, 95% CI 0.2-2.38; moderate certainty).[5] However, patients in this group had significantly longer duration of hospital stay (MD 4.80 days, 95% CI 3.06-6.54; moderate certainty), and length of ICU stay (MD 4.2 days, 95% CI 3.26-5.14; high certainty).[11]

Other Corticosteroids: Hydrocortisone, Methylprednisolone, and Prednisolone

The HCT group (RR 0.85, 95% CI 0.50-1.44; I^2=51%; moderate certainty)[1,3,11], MP group (RR 0.82, 95% CI 0.59-1.16; I^2=38%; moderate certainty)[4,5,7,9,12,13], and PRDL group (RR 0.63, 95% CI 0.21-1.92; moderate certainty)[6] did not show any significant difference in terms of all-cause mortality. Likewise, COVID-19-related mortality did not differ significantly between the use of IV methylprednisolone corticosteroid and standard of care (RR 1.04; 95% CI 0.29-3.73; moderate certainty).[15]

Similarly, included studies which utilized HP, MP, and PRDL did not demonstrate significant difference for a majority of the other outcomes; namely, all-cause mortality in 28 days (HR 0.80, 95% CI 0.24-2.61; low certainty)[15], COVID-19-related mortality in 28 days (HR 0.96, 95% CI 0.24-3.84; low certainty)[15], clinical improvement in 28 days (HR 0.93, 95% CI 0.65-1.33; I^2=0%; low certainty)[15,16], ICU admission (RR 0.78, 95% CI 0.32-1.90; I^2=0%; low certainty)[9,16], need for endotracheal intubation (RR 0.69, 95% CI 0.40-1.18; I^2=0%; low certainty)[4,9], eventual extracorporeal membrane oxygenation (RR 0.96, 95% CI 0.14-6.64; moderate certainty)[4], and life support-free days (MD -12.68, 95% CI -40.28-14.92; I^2=95%; low certainty).[6,14] Regarding length of hospital stay, one study showed that patients given PRDL had significantly shorter stays when compared with the control group (MD -0.90 days, 95% CI -1.56 to -0.24; low certainty).[9] The pooled data for length of hospital stay did not show a significant difference between the MP group and the control group (MD -0.28 days, 95% CI -1.62-1.07; I^2=93%; low certainty).[9,12,15]

Overall Adverse Events:

In terms of adverse events, there was no significant difference found between the IV corticosteroid and control groups (RR 0.95, 95% CI 0.86-1.05; I^2=0%; low certainty).[1,3-6,11] Specific adverse events such as development of nosocomial infection (RR 0.91, 95% CI 0.61-1.36; I^2=0%; low certainty)[4,8], shock (RR 0.17, 95% CI 0.01-3.32; low certainty)[8], need for insulin therapy (RR 1.20, 95% CI 0.99-1.46; moderate certainty)[9], and gastrointestinal symptoms (RR 0.91, 95% CI 0.47-1.78; I^2=0%; low certainty)[8,9] were likewise not significantly different between IV corticosteroids and control group or placebo.

Corticosteroids on Non-Oxygen-Requiring COVID-19 Patients

The RECOVERY Trial [13] provided a subgroup analysis on the mortality benefit of DEX among non-oxygen requiring COVID-19 patients. Result showed no 28-day mortality benefit and potential harm when DEX was given to COVID-19 patients who did not receive oxygen therapy at randomization (RR 1.19, 95% CI 0.92-1.55; moderate certainty).

Dosing of Corticosteroid: 12mg versus 6mg Dexamethasone

A multicenter, randomized controlled trial [19] assessed the effectiveness and safety of 12mg versus 6mg intravenous dexamethasone in 982 severe and critical COVID-19 patients. In this trial, 12mg dexamethasone (as intervention) was compared with the current standard dosing of 6mg (as control). Results showed marginal clinical benefit in terms of ventilator-free days (MD 1.00 day, 95% CI 0.21-1.79; high certainty), cardiovascular support-free days (MD 1.50 days, 95% CI 0.88-2.12; high certainty), and renal replacement therapy-free days (MD 1.10 days; 95% CI 0.66-1.54; high certainty) with the use of the 12mg dosing regimen. No significant difference was found in terms of all-cause mortality (RR 0.85, 95% CI 0.72-1.01; moderate certainty) and life support-free days (MD 2.80 days, 95% CI -0.20-5.8; moderate certainty). Development of any adverse event (RR 0.84, 95% CI 0.60-1.18; moderate certainty), septic shock (RR 0.82, 95% CI 0.55-1.21; moderate certainty), and invasive fungal infection (RR 0.70, 95% CI 0.36-1.33; moderate certainty) were also not significantly different between 12mg and 6mg dosing regimens. However, a trend towards developing clinically significant gastrointestinal bleeding (RR 1.76, 95% CI 0.59-5.20; moderate certainty) was associated with the 12mg dosing regimen. Thus, current evidence still supports the use of the 6mg dosing regimen of dexamethasone on the basis of inconclusive effect on all-cause mortality and marginal clinical benefit in terms of organ support-free days with the use of the 12mg dosing regimen.

Timing of Administration of Corticosteroids

Seven retrospective cohort studies [20-26] were reviewed to evaluate the effect of timing of administration of different corticosteroids on in-hospital mortality, need for mechanical ventilation, and development of adverse events among severe and critical COVID-19 patients. Corticosteroids used in the studies were dexamethasone 8-16mg IV or PO, hydrocortisone 45-100mg IV, methylprednisolone 50mg IV, and prednisone 10-80mg PO. Duration of treatment from day of trial enrollment ranged from seven to ten days. Timing of initiation of corticosteroids was stratified into early versus non-early. Different cut-off times for early versus non-early or delayed initiation were used across seven studies. Two studies [20,21] provided data for ≤24 hours versus >24 hours, two studies [20,22] provided data for ≤48 hours versus >48 hours, three studies [20,23,24] provided data for ≤72 versus >72 hours, and one study [25] provided data for ≤120 hours versus >120 hours. Significant benefit was found only when systemic corticosteroids were started early within 24 hours of diagnosis of severe to critical COVID-19 or of admission compared to non-early initiation beyond 24 hours (OR 0.68, 95% CI 0.51-0.92; I^2=0%; low certainty).[20,21] As initiation of systemic corticosteroids was further delayed at 48 hours (OR 0.98, 95% CI 0.78-1.24; I^2=0%; low certainty)[20,22], 72 hours (OR 1.01, 95% CI 0.81-1.25; I^2=0%; low certainty)[23,26,27], and 120 hours (OR 1.06, 95% CI 0.72-1.56; very low certainty)[25] from admission, mortality benefit became inconclusive. Use of mechanical ventilation was likewise significantly reduced when systemic corticosteroids were initiated within 24 hours of admission (OR 0.24, 95% CI 0.07-0.87; low certainty).[26] In terms of adverse events, initiation of systemic corticosteroids within the first 72 hours of admission showed higher rate of developing hyperglycemia (OR 6.94, 95% CI 3.80-12.67; low certainty) but did not result in significant development of blood stream infection (OR 1.69, 0.83-3.47; very low certainty), and hospital-acquired or ventilator-associated pneumonia (OR 1.45, 0.82-2.57; very low certainty).[24]

Summary of Certainty of Evidence

The certainty of evidence on the use of dexamethasone in severe and critical COVID-19 patients was downgraded to moderate certainty due to indirectness as one study [13] included patients who were given oral dexamethasone. The certainty of evidence on the use of dexamethasone in mild to moderate (non-oxygen) COVID-19 patients was downgraded to moderate certainty due to

serious imprecision. For the use of hydrocortisone, methylprednisolone, and prednisolone, certainty of evidence was low to moderate due to issues with blinding (in soft outcomes), inconsistency, indirectness, imprecision, and heterogeneity (see Appendix). Seven RCTs were either open-label trials or did not blind the personnel and the outcome assessors.[5,8-10,13-16] One RCT did not show the specific figures of the study results.[17] The data of two RCTs were extracted from the evidence review done by the WHO as their full articles could not be retrieved.[7] Certain outcomes, namely all-cause mortality (in HCT group)[4,6,14], length of hospital stay [9,11,12,15], and life support-free days [6,14] had significant heterogeneity (I^2>50%) in the pooled data.

In terms of dexamethasone dosing (12 mg versus 6 mg), certainty of evidence was downgraded to moderate certainty due to imprecision. Furthermore, publication bias may still be uncertain at this time as present evidence was based only on one published RCT. [19]

Cohort studies [20-26] which investigated the effect of timing of initiation of corticosteroids had very low overall certainty due to the inclusion of studies that lacked propensity matching and statistical adjustments on potential confounding variables, which had a serious impact on comparability between treatment groups.[24,25] As of 05 December 2021, no randomized controlled trial is currently available on this clinical question**.**

Evidence to Decision

From our literature search, one cost-effectiveness analysis on the use of DEX (6mg oral or IV) was found. The study done in South Africa shows that even though there was a cost increase with the addition of DEX to standard care, its cost still fell below willingness to pay thresholds and approaches 100% cost-effectiveness for thresholds beyond $500.[27] Locally, IV corticosteroids remain to be an economically viable drug as the daily cost of medication is below the average daily wage in the Philippines (₱263.77).[28,29]

Table 1. IV Corticosteroid Prices based on The Philippine Drug Price Reference Index [29]

Drug	Sample Regimen	Unit Price	Price/Regimen
Dexamethasone	20 mg/day x 5 days + 10 mg/day x 5 days	₱39.88 per ampule (5 mg/mL,1 mL ampule)	₱1,196.4
Hydrocortisone	100 mg every 6 hours x 7 days	₱21.06 per vial (100 mg powder, vial)	₱589.68
Methylprednisolone	40 mg BID x 3 days + 20 mg TID x 3 days	₱289.93 per vial (40 mg, single dose vial)	₱3,189.23

Intravenous corticosteroids are some of the most readily available drugs globally.[30] The WHO has listed DEX and PRDL as essential medicines; in the Philippines, DEX, HCT, MP, and PRDL are similarly recognized in the national formulary.[30,31] These drugs were deemed highly acceptable by the WHO due to their ease of administration, relatively short courses, and generally benign safety profile.[30]

Recommendations from Other Groups

The WHO's guidelines for COVID-19 therapeutics recommend the use of IV corticosteroids for severe or critical COVID-19. While there was still insufficient evidence for its effects on COVID-19 outcomes at that time, the panel claimed that clinicians were more confident in its safety profile compared to novel drugs. As its adverse effects are more familiar and more predictable, these can be monitored adequately by competent healthcare providers. For non-severe COVID-19, however, its use is not recommended as it was deemed unreasonable to obtain IV access just for

corticosteroids.[30] Treatment guidelines published by the US National Institutes of Health specifically recommend the use of DEX for hospitalized patients requiring supplemental oxygen as there was no significant benefit found in patients on room air. In the absence of DEX, other IV corticosteroids are recommended as replacement (HCT, MP, Prednisone).[32]

Research Gaps

As of November 24, 2021, there are 14 ongoing RCTs on IV corticosteroid use for COVID-19 registered on ClinicalTrials.gov: 2 trials for IV corticosteroid vs. standard of care or placebo, five trials for two IV corticosteroids, five trials for different doses of the same IV corticosteroid, two trials for different timing of IV corticosteroid administration.

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Appendix 1. Evidence to Decision

Table 2. Summary of initial judgements prior to the panel discussion (N=6)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)				• COVID-19 patients are at risk for ICU admission. IV corticosteroids are staple critical care medications that are easily accessible.
Benefits	Large (4)	Moderate (2)	Small	Uncertain		• Dexamethasone significantly decreased all-cause mortality in COVID-19 patients.
Harm	Large (2)	Small (4)	Uncertain	No response		• Adverse events are comparable between the IV corticosteroid group and the control group as well as between the different doses of Dexamethasone. • Incidence of hyperglycemia was significantly found in early initiation of corticosteroids (less than 72 hours). Development of blood stream infection, hospital-acquired pneumonia, and ventilator-acquired pneumonia were comparable between early and later initiation of corticosteroids.
Certainty of Evidence	High	Moderate (5)	Low (1)	Very low		• Low to very low
Balance of effects	Favors drug (6)	Does not favor drug	Uncertain			**Type and Dosing of Corticosteroids** • Favors IV Corticosteroids: All-cause Mortality, All-cause Mortality (Dexamethasone Group), Ventilator-free Days, WHO Ordinal Scale • Favors Control: Length of ICU Stay **Timing of Corticosteroids** • Favors Early Initiation at 24 hours of Admission: Decreased mortality and decreased odds of mechanical intubation

Values	Important uncertainty or variability	Possibly important uncertainty or variability	Possibly NO important uncertainty or variability (6)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (2)	Negligible cost (4)	Moderate savings	Large savings	• IV Corticosteroids are relatively affordable and easily accessible in most government hospitals.
Certainty of evidence of required resources	No included studies	Very low	Low	Moderate (6)	High		• Moderate • Cost-effectiveness analysis: high willingness-to-pay thresholds ($3015 per disability-adjusted life years).
Cost effectiveness	No included studies	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (5)			• The cost-effectiveness analysis favors the addition of Dexamethasone to standard care.
Equity	Uncertain	Reduced	Probably no impact (4)	Increased (2)			
Acceptability	Uncertain	No	Yes (4)				
Feasibility	Uncertain (1)	No	Yes (5)				

Appendix 2. Search Strategy & Results

Table 3A. Search Yield for Type and Dosing of Corticosteroids

#	Query	Results
1	“corticosteroids”	1,208,536
2	“intravenous” OR “IV” OR “systemic”	10,316,134
3	“dexamethasone” OR “hydrocortisone” OR “methylprednisolone”	960,504
4	“high dose” OR “low dose”	5,053,226
5	“SARS-CoV-2” OR “COVID-19”	4,611,326
6	“severe” OR “critical”	10,304,491
7	“mortality”	5,415,850
8	“hospital length of stay” OR “ICU length of stay” OR “mechanical ventilation” OR “organ support-free days” OR “adverse events” OR “infection” OR “superinfection” OR “hyperglycemia” OR “gastrointestinal bleeding”	4,115,119
9	#1 AND #2	763,571
10	#3 OR #9	930,619
11	#4 OR #10	1,024,552
12	#5 AND #6	3,647,875
13	#7 OR #8	3,021,395
14	#11 AND #12 AND #13	**20,339**

Figure 1A. PRISMA Flow Diagram for Type and Dosing of Corticosteroids

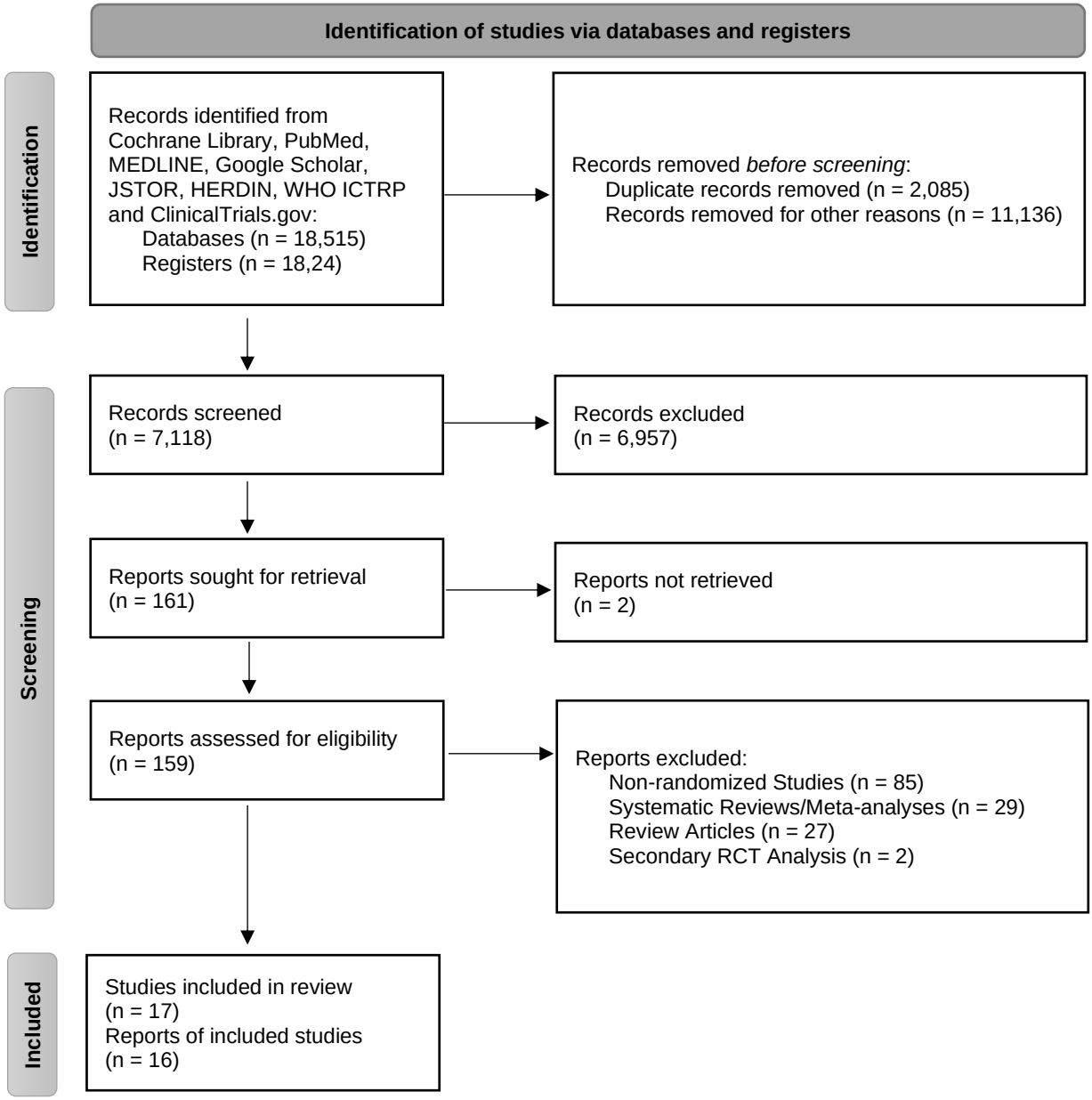
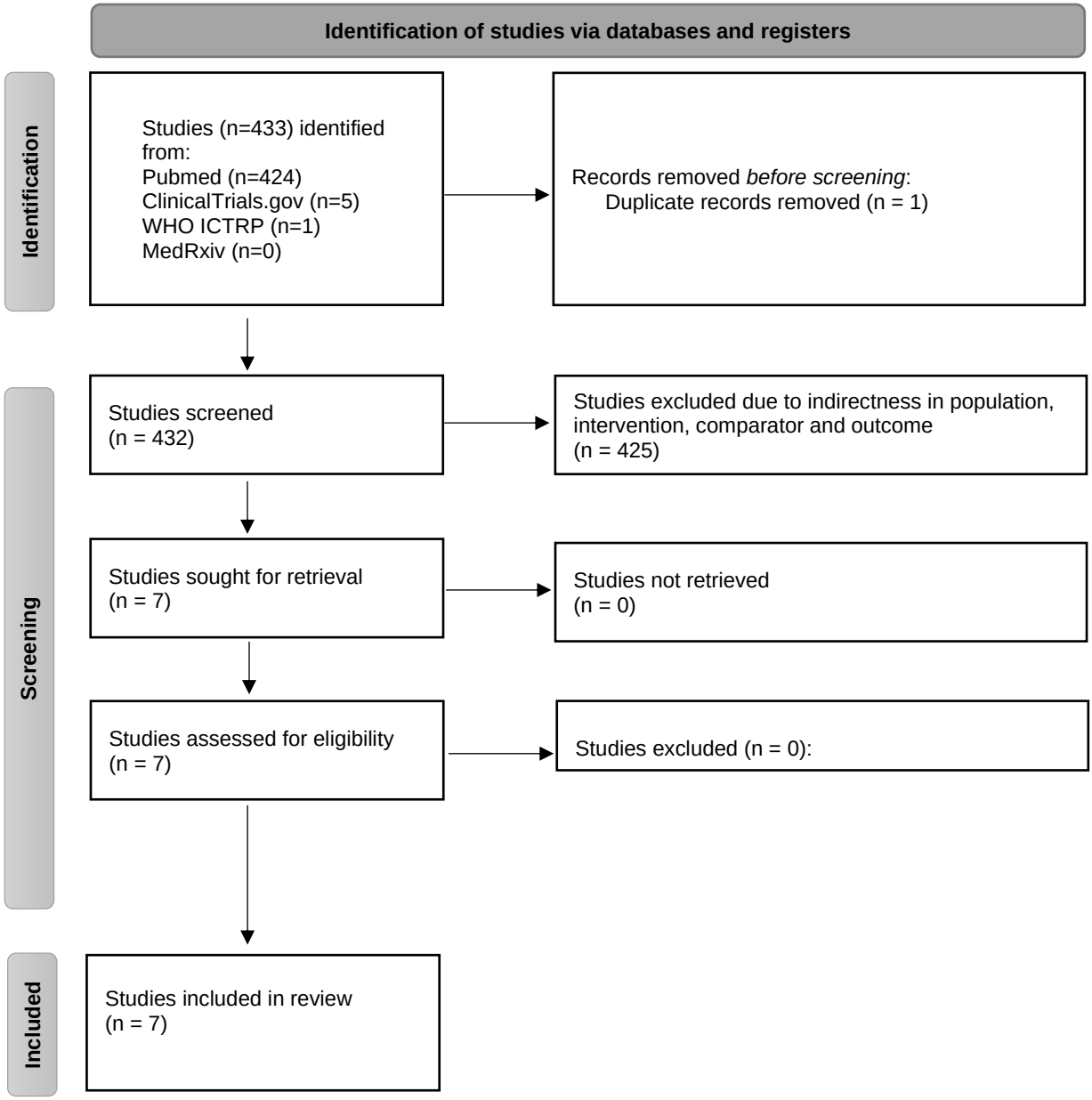


Table 3B. Search Yield for Timing of Corticosteroids

Search	Query	Results	Time
#6	Search: **((corticosteroids) AND (COVID-19)) AND ((early) OR (timing))** ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("early"[All Fields] OR ("timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields])) **Translations** **corticosteroids:** "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields] **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) **timing:** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	424	23:22:58
#5	Search: **(early) OR (timing)** "early"[All Fields] OR "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields] **Translations** **timing:** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	1,909,206	23:22:47
#4	Search: **timing** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields] **Translations** **timing:** "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	226,302	23:22:38
#3	Search: **early** "early"[All Fields]	1,730,924	23:22:29
#2	Search: **COVID-19** "covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19	202,271	23:22:04

	nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) **Translations** **COVID-19:** ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))		
#1	Search: **corticosteroids** "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields] **Translations** **corticosteroids:** "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields]	364,476	23:21:54

Figure 1B. PRISMA Flow Diagram for Timing of Corticosteroids



Appendix 3. Included Studies

Table 4A. Characteristics of Included Studies for Type and Dosing of Corticosteroids

Study ID	Patients (n)	Interventions	Outcomes	Method
CAPE COVID 2020	Critically-ill COVID-19 patients (n = 149)	Hydrocortisone (200 mg/day until day 7, then 100 mg/day x 4 days, then 50 mg/day x 3 days)	All-cause Mortality, Intubation Rate, ECMO Rate, Adverse Events, Nosocomial Infection	Multicenter Randomized Double-blind Trial
CoDEX 2020	COVID-19 patients with moderate to severe ARDS (n = 299)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	All-cause Mortality, Ventilator-free Days, SOFA Score	Multicenter Randomized Open-label Trial
COVID STEROID 2021	COVID-19 patients with severe hypoxia (n = 30)	Hydrocortisone (200 mg/day)	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Blinded Trial
COVID STEROID 2 2021	COVID-19 patients with severe hypoxemia (n = 982)	Dexamethasone (12 or 6 mg/day)	All-cause Mortality, Life Support-free Days, Ventilator-free Days, Cardiovascular Support-free Days, Renal Replacement Therapy-free Days, Adverse Events	Multicenter Randomized Blinded Trial
DEXA-COVID 19 2020	COVID-19 patients with moderate to severe ARDS (n = 19)	Dexamethasone (20 mg/day × 5 days, then 10 mg/day × 5 days)	All-cause Mortality, Adverse Events	Multicenter Randomized Open-label Trial

Edalatifard 2020	patients with severe COVID-19 (n = 62)	Methylprednisolone (250 mg/day x 3 days)	All-cause Mortality, Adverse Events, Nosocomial Infection, Shock, GI Symptoms	Multicenter Randomized Single-blind Trial
Farahani 2020	COVID-19 patients with severe respiratory failure (n = 29)	Methylprednisolone (1000 mg/day x 3 days)	GCS	Single-center Randomized Double-blind Trial
Ghanei 2021	patients with severe COVID-19 (n = 336)	Prednisolone (25 mg/day)	All-cause Mortality, Length of Hospital Stay, Admission to ICU, Intubation Rate, Adverse Events, GI Symptoms	Multicenter Randomized Open-label Trial
GLUCOCOVID 2021	patients with severe COVID-19 (n = 64)	Methylprednisolone (40 mg BID x 3 days, then 20 mg TID x 3 days)	All-cause Mortality	Multicenter Randomized Open-label Trial
Jamaati 2021	COVID-19 patients with mild to moderate ARDS (n = 50)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	All-cause Mortality, Length of Hospital Stay, Length of ICU Stay, SOFA Score	Single-center Randomized Trial
Jeronimo 2021	patients with severe COVID-19 (n = 393)	Methylprednisolone (0.5 mg/kg/day)	All-cause Mortality, Length of Hospital Stay, Need for Insulin Therapy	Single-center Randomized Double-blind Trial
Ranjbar 2021	COVID-19 patients severe (n = 90)	Dexamethasone (6 mg/day) Methylprednisolone (2 mg/kg/day)	WHO Ordinal Scale	Single-center Randomized Triple-blind Trial
RECOVERY 2021	COVID-19 patients (n = 6,425)	Dexamethasone (6 mg/day x 10 days)	All-cause Mortality	Multicenter Randomized Open-label Trial
REMAP-CAP 2020	patients with severe COVID-19 (n = 379)	Hydrocortisone Fixed 7-day Course (50 mg or 100 mg every 6 hours)	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Open-label Trial

		Hydrocortisone Shock-Dependent Course (50 mg or 100 mg every 6 hours when in shock)		
Solanich 2021	patients with severe COVID-19 (n = 55)	Methylprednisolone (120 mg/day x 3 days)	All-cause Mortality, COVID-19-related Mortality, Time to Death (All-cause), Time to Death (COVID-19-related), Time to Clinical Improvement, Length of Hospital Stay	Single-center Randomized Open-label Trial
Steroids-SARI 2020	ICU-admitted COVID-19 patients (n = 47)	Methylprednisolone (40 mg every 12 hours × 5 days)	All-cause Mortality, Adverse Events	Single-center Randomized Open-label Trial
Tang 2021	COVID-19 patients with CT-confirmed pneumonia (n = 86)	Methylprednisolone (1 mg/kg/day)	All-cause Mortality, Time to Clinical Improvement, Admission to ICU	Multicenter Randomized Single-blind Trial

Table 4B. Characteristics of Included Studies for Timing of Corticosteroids

Study ID	Patients (n)	Interventions	Comparator	Outcomes
Bahl A, Johnson S, Chen NW. Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients. Intern Emerg Med. 2021 Sep;16(6):1593-1603. doi: 10.1007/s11739-021-02655-6. Epub 2021 Feb 5. PMID: 33547620; PMCID: PMC7864133.[23]	Severe COVID-19 Hypoxia (n=615)	Timing: <24 Hours Timing: <48 Hours Timing: <72 Hours (n=371) Dexamethasone 8-16 mg IV/PO Hydrocortisone 45-100 mg IV Methylprednisolone 1-50 mg IV Prednisone 10-80 mg PO Plus Standard of Care	Timing: >24 Hours Timing: >48 Hours Timing: >72 Hours (n=244) Dexamethasone 8-16 mg IV/PO Hydrocortisone 45-100 mg IV Methylprednisolone 1-500 mg IV Prednisone 10-80 mg PO Plus Standard of Care	In-hospital Mortality
Sulaiman K, Al Juhani O, Korayen GB, Eljaaly K, Alhubaishi A, Al Harbi O, Badreldin HA, Al Yousif GA, Vishwakarma R, Altebainawi A, Albelwi S, Almutairi R, Almousa M, Alghamdi R, Alharbi A, Algami R, Akhani N, Al Hartin A, Alissa A, Al Homaid S, Al Qahtani K, Al Atassi A, Al Ghamdi G. Early Versus Late Use of Dexamethasone in Critically Ill Patients	Severe and critical COVID-19 (n=202)	Timing: <24 Hours *24 hours within ICU admission (n=101) Dexamethasone 6 mg Methylprednisolone Plus Standard of Care	Timing: >24 Hours *24 hours within ICU admission (n=101) Dexamethasone 6 mg Methylprednisolone Plus Standard of Care	In-hospital Mortality

with COVID-19: A Multicenter, Cohort Study. ResearchSquare [Preprint]. 2021 Jul 26 [cited 2021 Nov 27]. Available from https://www.researchsquare.com/article/rs-349677/v1 [24]				
Monedero P, Gea A, Castro P, Candela-Toha AM, Hernández-Sanz ML, Arruti E, Villar J, Ferrando C; COVID-19 Spanish ICU Network. Early corticosteroids are associated with lower mortality in critically ill patients with COVID-19: a cohort study. Crit Care. 2021 Jan 4;25(1):2. doi: 10.1186/s13054-020-03422-3. PMID: 33397463; PMCID: PMC7780210. [25]	Severe and critical COVID-19 (n=691)	Timing: <48 Hours (n=485) Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	Timing: >48 Hours (n=206) Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	In-hospital Mortality Adverse Events

Akhtar H, Khalid S, Rahman FU, Ali S, Afridi M, Khader YS, Hassan F, Akhtar N, Khan MM, Ikram A. Delayed admissions and efficacy of steroid use in patients with critical and severe COVID-19: an apprehensive approach. J Public Health (Oxf). 2021 Sep 27:fdab239. doi: 10.1093/pubmed/fdab239. [26]	Severe and critical COVID-19 (n=659)	Timing: <72 Hours (n=321) Cut off: 5 days from admission onset Type of steroid not specified Plus Standard of Care	Timing: >72 Hours (n=338) Type of steroid not specified Plus Standard of Care	In-hospital Mortality
Dupuis C, de Montmollin E, Buetti N, Goldgran-Toledano D, Reignier J, Schwebel C, Domitile J, Neuville M, Ursino M, Siami S, Ruckly S, Alberti C, Mourvillier B, Bailly S, Laurent V, Gainnier M, Souweine B, Timsit JF; OutcomeReaTM research network. Impact of early corticosteroids on 60-day mortality in critically ill patients	Severe and critical COVID-19 (n=303)	Timing: <72 Hours (n=66) Dexamethasone HSHC Methylprednisolone Prednisolone Plus Standard of Care	Timing: >72 Hours (n=237) Dexamethasone HSHC Methylprednisolone Prednisolone Plus Standard of Care	In-hospital Mortality Adverse Events Hyperglycemia Infection

with COVID-19: A multicenter cohort study of the OUTCOMEREA network. PLoS One. 2021 Aug 4;16(8):e0255644. doi: 10.1371/journal.pone.0255644. PMID: 34347836; PMCID: PMC8336847. [27]				
Moreno A, Vargas C, Azocar F, Villarroel F, Cofré M, Oppliger H, Ríos F, Raijmakers M, Silva-Ayarza I, Beltrán C, Zamora F. Steroids and mortality in non-critically ill COVID-19 patients: a propensity score-weighted study in a Chilean cohort. Int J Infect Dis. 2021 Sep 20;112:124-129. doi: 10.1016/j.ijid.2021.09.038. Epub ahead of print. PMID: 34547488; PMCID: PMC8450146. [28]	Severe and critical COVID-19 (n=520)	Timing: <120 Hours (n=233) Initiation from start of symptoms: Early: 9 days (7-12) days Duration Early: 2-4 days Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	Timing: >120 Hours (n=287) Initiation from start of symptoms: Non-Early: 10 days 10-16 days) Duration Early: 2-4 days Dexamethasone Methylprednisolone Prednisone Plus Standard of Care	In-hospital Mortality

Li Y, Zhou X, Li T, Chan S, Yiqi Y, Ai JW, Zhang H, Sun F, Zhang Q, Zhu L, Shao L, Xu B, Zhang W. Corticosteroid prevents COVID-19 progression within its therapeutic window: a multicentre, proof-of-concept, observational study, Emerg. Microbes Infect., 9:1, 1869-1877, DOI: 10.1080/22221751.2020.1807885 [29]	Severe to critical COVID-19 High risk for progressing to ARDS (n=68)	Timing: <24 Hours (n=47) Methylprednisolone 40-80 mg/day for 3 days then 20 mg/day with a total treatment period of less than 7 days Plus Standard of Care	Timing: >72 Hours (n=41) Methylprednisolone 40-80 mg/day for 3 days then 20 mg/day with a total treatment period of less than 7 days Plus Standard of Care	Need for Mechanical Ventilation

Appendix 4. Risk of Bias Assessment

Figure 2A. Risk of Bias Graph for Type and Dosing of Corticosteroids

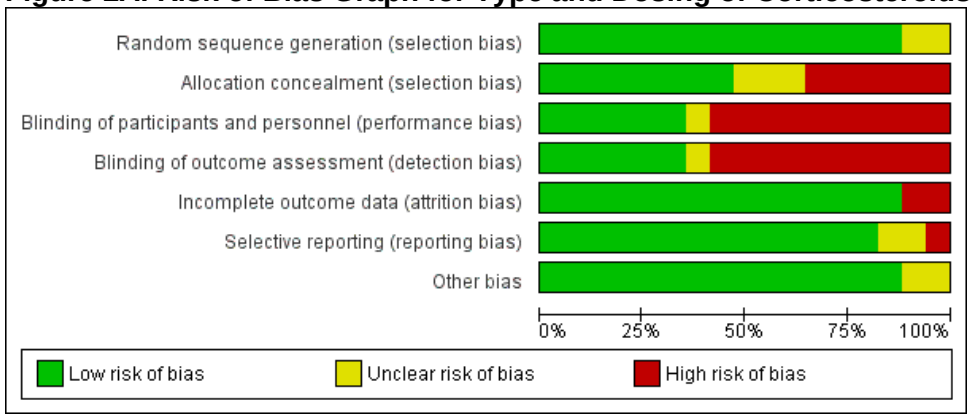


Figure 2B. Risk of Bias Summary for Type and Dosing of Steroids

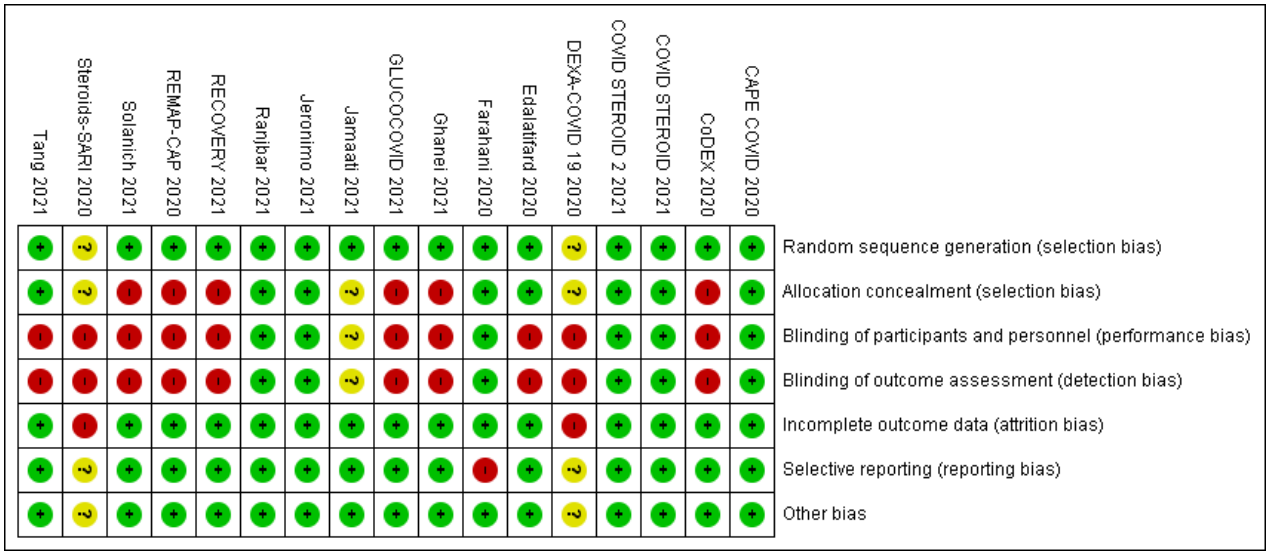


Figure 3A. Risk of Bias Graph for Timing of Corticosteroids

Figure 3B. Risk of Bias Summary for Timing of Corticosteroids Using Newcastle Ottawa Scale

		Akhtar 2021	Bahl 2021	Dupuis 2021	Hyun 2021	Li 2021	Monedero 2021	Moreno 2021	Sulaiman 2021
A	**Selection**								
	Representative of exposed cohort	+	+	+	+	+	+	+	+
	Selection of the non-exposed cohort from the same community as exposed cohort	+	+	+	+	+	+	+	+
	Ascertainment of exposure by secure record	+	+	+	+	+	+	+	+
	Demonstration that outcome of interest was not present at the start of the study	+	+	+	+	+	+	+	+
B	**Comparability**								
	Study controls for other variables	+	+	−	−	+	+	−	+
C	**Outcome**								
	Assessment of outcome	+	+	+	+	+	+	+	+
	Follow-up long enough for outcome to occur	+	+	+	+	+	+	+	+
	Complete follow up of all subjects accounted for	+	+	−	+	+	+	+	+

Legend:
+ Low risk of bias
? Unclear risk of bias
− High risk of bias

Appendix 5.1. GRADE Evidence Profile for Type and Dosing of Corticosteroids

Question: Should intravenous corticosteroids be used in COVID-19?
Patient or Population: Moderately to Critically-Ill COVID-19 Patients
Setting: In-patients Setting
Intervention: Intravenous Corticosteroids
Comparison: Standard Care or Placebo

Table 5. Summary of Findings Table (IV Corticosteroids vs. Standard Care or Placebo)

Certainty Assessment							№ of Patients		Effect		Certainty
№ of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	IV Corticosteroids	Control	Relative (95% CI)	Absolute (95% CI)	
All-cause Mortality (All Corticosteroids)											
14	randomized trials	not serious	not serious	serious[c]	not serious	none	703/2629 (26.7%)	1269/4230 (30.0%)	**RR 0.87** (0.78 to 0.97)	**39 fewer per 1,000** (from 66 fewer to 9 fewer)	⊕⊕⊕◯ MODERATE
All-cause Mortality (Dexamethasone Group)											
4	randomized trials	not serious	not serious	serious[c]	not serious	none	497/1786 (27.8%)	1079/3472 (31.1%)	**RR 0.86** (0.79 to 0.94)	**44 fewer per 1,000** (from 65 fewer to 19 fewer)	⊕⊕⊕◯ MODERATE
All-cause Mortality (Hydrocortisone Group)											
3	randomized trials	not serious	not serious	not serious	serious[d,e]	none	96/369 (26.0%)	56/188 (29.8%)	**RR 0.85** (0.50 to 1.44)	**45 fewer per 1,000** (from 149 fewer to 131 more)	⊕⊕⊕◯ MODERATE
All-cause Mortality (Methylprednisolone Group)											
4	randomized trials	not serious	not serious	not serious	serious[d]	none	106/357 (29.7%)	122/350 (34.9%)	**RR 0.82** (0.59 to 1.16)	**63 fewer per 1,000** (from 143 fewer to 56 more)	⊕⊕⊕◯ MODERATE

Certainty Assessment							№ of Patients		Effect		Certainty
№ of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	IV Corticosteroids	Control	Relative (95% CI)	Absolute (95% CI)	
All-cause Mortality (Prednisolone Group)											
1	randomized trials	not serious	not serious	not serious	serious[d]	none	4/116 (3.4%)	12/220 (5.5%)	**RR 0.63** (0.21 to 1.92)	**20 fewer per 1,000** (from 43 fewer to 50 more)	⊕⊕⊕◯ MODERATE
COVID-19-related Mortality											
1	randomized trials	not serious	not serious	not serious	serious[d,f,g]	none	4/27 (14.8%)	4/28 (14.3%)	**RR 1.04** (0.29 to 3.73)	**6 more per 1,000** (from 101 fewer to 390 more)	⊕⊕⊕◯ MODERATE
Time to Death (All-cause)											
1	randomized trials	not serious	not serious	not serious	serious[d]	none	27 participants	28 participants	**HR 0.80** (0.24 to 2.61)	--	⊕⊕⊕◯ MODERATE
Time to Death (COVID-19-related)											
1	randomized trials	not serious	not serious	not serious	serious[d]	none	27 participants	28 participants	**HR 0.96** (0.24 to 3.84)	--	⊕⊕⊕◯ MODERATE
Time to Clinical Improvement											
2	randomized trials	serious[a]	not serious	not serious	serious[d]	none	70 participants	71 participants	**HR 0.93** (0.65 to 1.33)	--	⊕⊕◯◯ LOW
Length of Hospital Stay (Dexamethasone)											
1	randomized trials	not serious	not serious	not serious	serious[f]	none	25	35	--	MD **4.80 day higher** (3.06 higher to 6.54 higher)	⊕⊕⊕◯ MODERATE
Length of Hospital Stay (Methylprednisolone and Prednisolone)											
3	randomized trials	serious[a]	not serious	not serious	serious[d,e]	none	337	406	--	MD **0.28 day lower** (1.62 lower to 1.07higher)	⊕⊕◯◯ LOW
ICU Admission											
2	randomized trials	serious[a]	not serious	not serious	serious[d]	none	7/159 (4.4%)	15/263 (5.7%)	**RR 0.78** (0.32 to 1.90)	**13 fewer per 1,000** (from 39 fewer to 51 more)	⊕⊕◯◯ LOW
Length of ICU Stay											
1	randomized trials	not serious	not serious	not serious	not serious	none	25	25	--	MD **4.2 days more** (3.26 more	⊕⊕⊕⊕ HIGH

										to 5.14 more)	

Certainty Assessment							№ of Patients		Effect		Certainty
№ of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**IV Corticosteroids**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**	
Intubation Rate											
2	randomized trials	serious[a]	not serious	not serious	serious[d]	none	10/132 (7.6%)	16/236 (6.8%)	**RR 0.69** (0.40 to 1.18)	**21 fewer per 1,000** (from 41 fewer to 12 more)	⊕⊕◯◯ LOW
ECMO Rate											
1	randomized trials	not serious	not serious	not serious	serious[d,g]	none	2/76 (2.6%)	2/73 (2.7%)	**RR 0.96** (0.14 to 6.64)	**1 fewer per 1,000** (from 24 fewer to 155 more)	⊕⊕⊕◯ MODERATE
Life Support-free Days											
2	randomized trials	serious[a]	not serious	not serious	serious[d]	none	294	115	--	MD **12.68 days fewer** (40.28 fewer to 14.92 more)	⊕⊕◯◯ LOW
Ventilator-free Days											
1	randomized trials	serious[a]	not serious	not serious	not serious	none	151	148	--	MD **2.26 days more** (0.2 more to 4.38 more)	⊕⊕⊕◯ MODERATE
SOFA Score											
2	randomized trials	serious[a]	not serious	not serious	serious[d]	none	152	145	--	MD **0.49 points lower** (2.18 lower to 1.2 higher)	⊕⊕◯◯ LOW
Adverse Events											
7	randomized trials	serious[a,b]	not serious	not serious	serious[d]	none	113/538 (21.0%)	168/461 (36.4%)	**RR 0.95** (0.86 to 1.05)	**18 fewer per 1,000** (from 51 fewer to 18 more)	⊕⊕◯◯ LOW

Certainty Assessment							№ of Patients		Effect		Certainty
№ of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**IV Corticosteroids**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**	
Nosocomial Infection											
2	randomized trials	serious[a]	not serious	not serious	serious[d]	none	29/110 (26.4%)	30/101 (29.7%)	**RR 0.91** (0.61 to 1.36)	**27 fewer per 1,000** (from 116 fewer to 107 more)	⊕⊕◯◯ LOW
Shock											
1	randomized trials	serious[a]	not serious	not serious	serious[d,f,g]	none	0/34 (0.0%)	2/28 (7.1%)	**RR 0.17** (0.01 to 3.32)	**59 fewer per 1,000** (from 71 fewer to 166 more)	⊕⊕◯◯ LOW
Need for Insulin Therapy											
1	randomized trials	not serious	not serious	not serious	serious[d]	none	103/173 (59.5%)	86/174 (49.4%)	**RR 1.20** (0.99 to 1.46)	**99 more per 1,000** (from 5 fewer to 227 more)	⊕⊕⊕◯ MODERATE
Gastrointestinal Symptoms											
2	randomized trials	serious[a]	not serious	not serious	serious[d]	none	12/148 (8.1%)	23/236 (9.7%)	**RR 0.91** (0.47 to 1.78)	**9 fewer per 1,000** (from 52 fewer to 76 more)	⊕⊕◯◯ LOW

CI: Confidence interval; **HR**: hazard Ratio; **MD**: mean difference; **RR**: relative risk

Explanations

a. Some included studies were open-label trials.
b. Data from some RCTs were retrieved from a systematic review.
c. One study used both oral and IV DEX.
d. Confidence interval crossed the threshold.
e. Pooled data showed significant heterogeneity.
f. The study had low event rates within a small population.
g. The result had a wide confidence interval.

Table 6. Summary of Findings Table (Dexamethasone 12 mg vs. 6 mg)

Certainty Assessment							№ of Patients		Effect		Certainty
№ of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**DEX 12 mg**	**DEX 6 mg**	**Relative (95% CI)**	**Absolute (95% CI)**	
All-cause Mortality											
1	randomized trials	not serious	not serious	not serious	serious[a]	none	157/490 (32.0%)	180/478 (37.7%)	**RR 0.85** (0.72 to 1.01)	**56 fewer per 1,000** (from 105 fewer to 4 more)	⊕⊕⊕◯ MODERATE
Life Support-free Days											
1	randomized trials	not serious	not serious	not serious	serious[a]	none	489	478	--	MD **2.8 days more** (0.2 fewer to 5.8 more)	⊕⊕⊕◯ MODERATE
Ventilator-free Days											
1	randomized trials	not serious	not serious	not serious	not serious	none	491	480	--	MD **1 days more** (0.21 more to 1.79 more)	⊕⊕⊕⊕ HIGH
Cardiovascular Support-free Days											
1	randomized trials	not serious	not serious	not serious	not serious	none	491	480	-	MD **1.5 days more** (0.88 more to 2.12 more)	⊕⊕⊕⊕ HIGH
Renal Replacement Therapy-free Days											
1	randomized trials	not serious	not serious	not serious	not serious	none	491	480	-	MD **1.1 days more** (0.66 more to 1.54 more)	⊕⊕⊕⊕ HIGH
Adverse Events											
1	randomized trials	not serious	not serious	not serious	serious[a]	none	56/497 (11.3%)	65/485 (13.4%)	**RR 0.84** (0.60 to 1.17)	**21 fewer per 1,000** (from 54 fewer to 23 more)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **MD**: mean difference; **RR**: relative risk

Explanations

a. Confidence interval crossed the threshold.

Appendix 5.2. GRADE Evidence Profile for Timing of Corticosteroids

Question: Should early versus non-early initiation of intravenous corticosteroids be used in COVID-19?
Patient or Population: Severe and critical COVID-19 patients
Setting: In-patients Setting
Intervention: Early Initiation of Corticosteroids
Comparison: Non-early Initiation of Corticosteroids

Table 7. Summary of Findings Table (Early versus Non-Early Initiation of Corticosteroids)

Certainty Assessment							№ of Patients		Effect		Certainty	Importance
№ of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Early Corticosteroids	Non-Early Corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality (Intervention Cutoff: 24 Hours)												
2	observational studies	not serious	not serious	not serious	not serious	none	107/307 (34.9%)	212/510 (41.6%)	**OR 0.68** (0.51 to 0.92)	**90 fewer per 1,000** (from 149 fewer to 20 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality (Intervention Cutoff: 48 Hours)												
2	observational studies	not serious	not serious	not serious	not serious	none	366/786 (46.9%)	223/520 (42.9%)	**OR 0.98** (0.78 to 1.24)	**5 fewer per 1,000** (from 59 fewer to 53 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mortality (Intervention Cutoff: 72 Hours)												
3	observational studies	serious[a]	not serious	not serious	not serious	none	380/758 (50.1%)	397/819 (48.5%)	**OR 1.01** (0.81 to 1.25)	**2 more per 1,000** (from 52 fewer to 56 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality (Intervention Cutoff: 120 Hours)												
1	observational studies	not serious	not serious	not serious	serious[b]	none	67/233 (28.8%)	79/287 (27.5%)	**OR 1.06** (0.72 to 1.56)	**12 more per 1,000** (from 61 fewer to 97 more)	⊕◯◯◯ VERY LOW	CRITICAL
Need for Mechanical Ventilation												
1	observational studies	not serious	not serious	not serious	not serious	none	5/47 (10.6%)	7/21 (33.3%)	**OR 0.24** (0.07 to 0.87)	**226 fewer per 1,000** (from 300 fewer to 30 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **MD**: mean difference

Explanations
a. Lack of propensity matching and statistical adjustment for potential confounders (Dupuis et al., 2021)
b. Wide confidence interval
c. Small population and small event rates

Certainty Assessment							№ of Patients		Effect		Certainty	Importance
№ of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Early Corticosteroids**	**Non-Early Corticosteroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse Events: Hyperglycemia												
1	observational studies	not serious	not serious	not serious	not serious	none	46/66 (69.7%)	59/237 (24.9%)	**OR 6.94** (3.80 to 12.67)	**448 more per 1,000** (from 308 more to 599 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse Events: Blood Stream Infection												
1	observational studies	not serious	not serious	not serious	serious[b]	none	13/66 (19.7%)	30/237 (12.7%)	**OR 1.69** (0.83 to 3.47)	**70 more per 1,000** (from 19 fewer to 208 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse Events: Incidence of Hospital-Acquired Pneumonia and Ventilator Acquired Pneumonia												
1	observational studies	not serious	not serious	not serious	serious[b]	none	23/66 (34.8%)	70/237 (29.5%)	**OR 1.45** (0.82 to 2.57)	**83 more per 1,000** (from 40 fewer to 223 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD**: mean difference

Explanations

a. Lack of propensity matching and statistical adjustment for potential confounders (Dupuis et al., 2021)
b. Wide confidence interval
c. Small population and small event rates

Appendix 6. Forest Plots

Figure 4. All-Cause Mortality Forest Plot for Type and Dosing of Corticosteroids

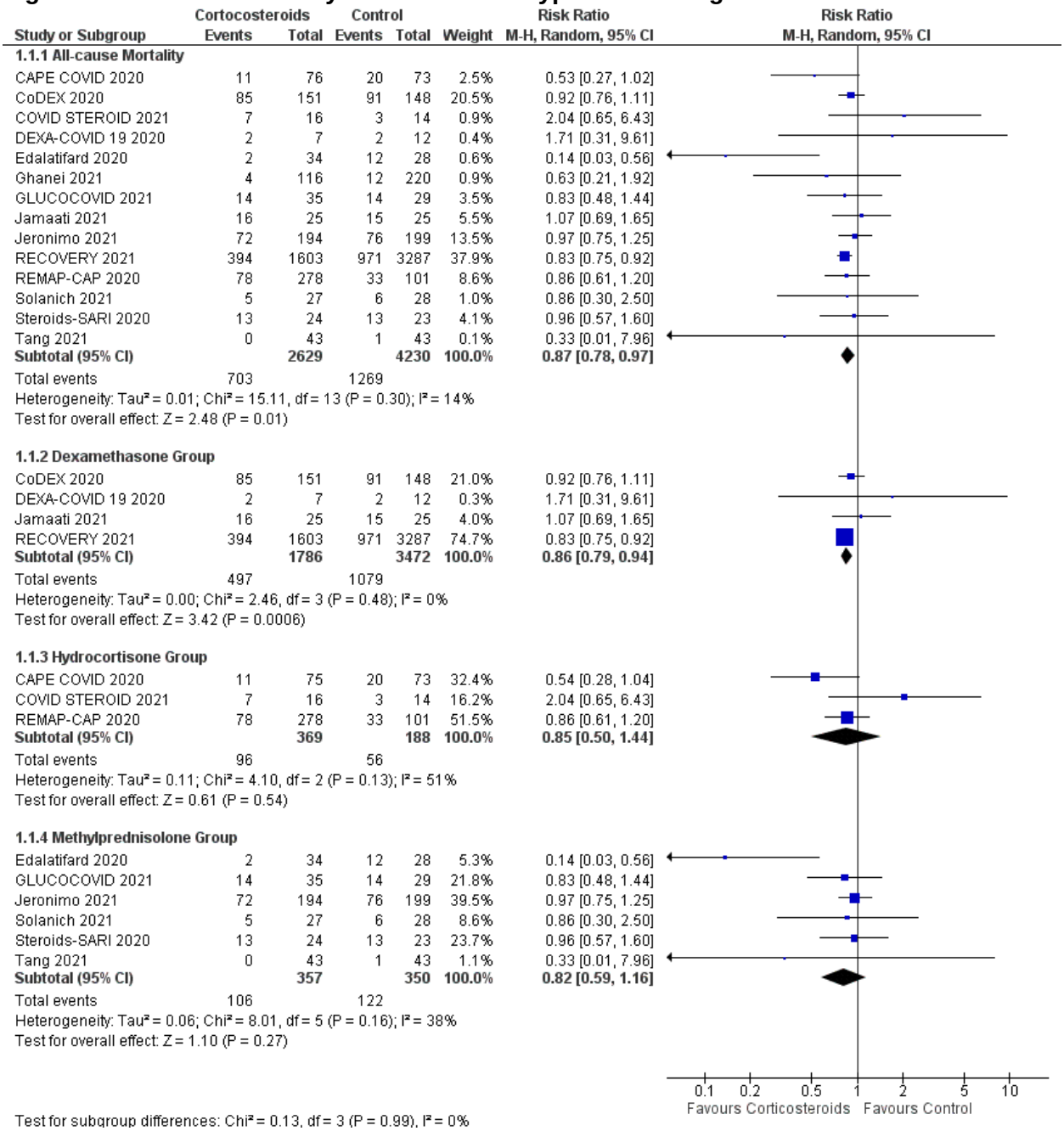


Figure 5. Time to Clinical Improvement Forest Plot for Type and Dosing of Corticosteroids

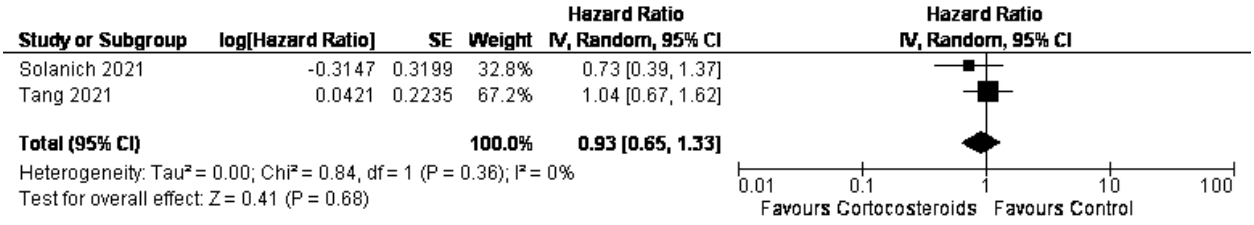


Figure 6. Length of Hospital Stay Forest Plot for Type and Dosing of Corticosteroids

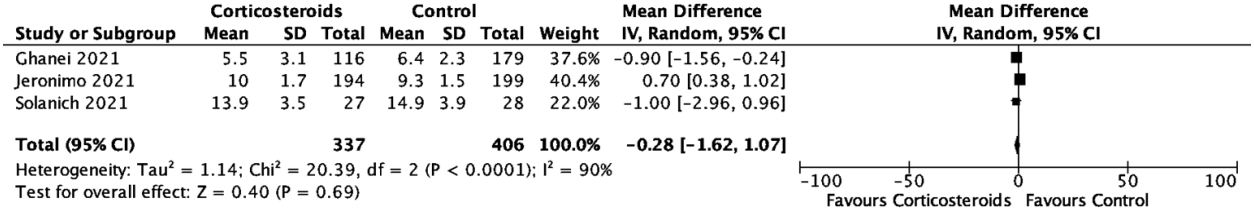


Figure 7. ICU Admission Forest Plot for Type and Dosing of Corticosteroids

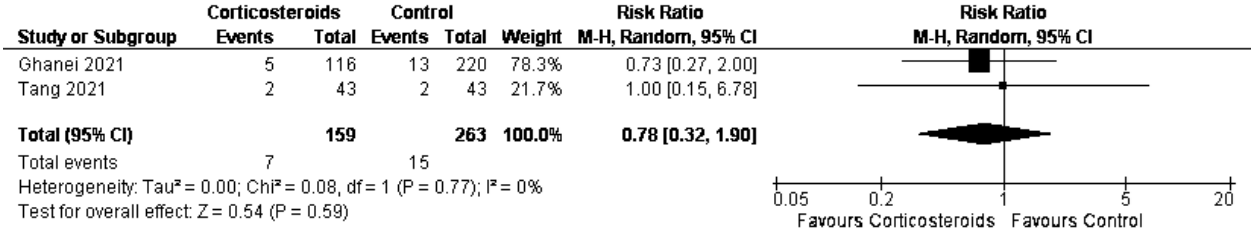


Figure 8. Intubation Rate Forest Plot for Type and Dosing of Corticosteroids

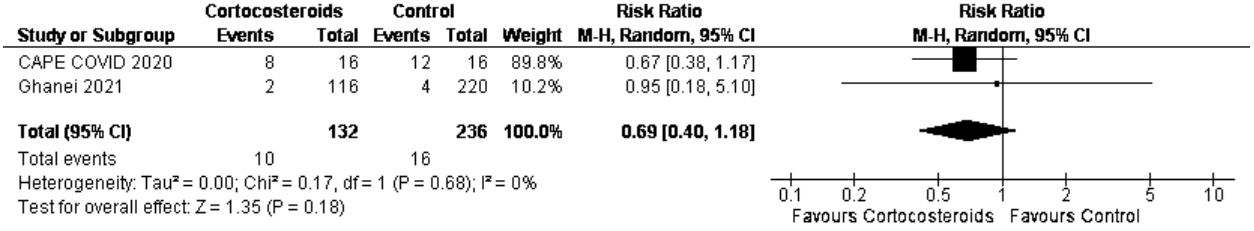


Figure 9. Life Support-free Days Forest Plot for Type and Dosing of Corticosteroids

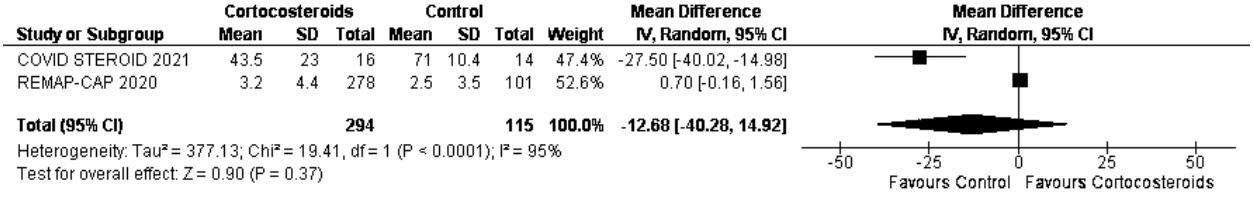


Figure 10. SOFA Score Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Cortocosteroids Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
CoDEX 2020	6.1	3.4168	127	7.5	3.3194	120	47.4%	-1.40 [-2.24, -0.56]
Jamaati 2021	4.73	0.65	25	4.4	0.52	25	52.6%	0.33 [0.00, 0.66]
Total (95% CI)			**152**			**145**	**100.0%**	**-0.49 [-2.18, 1.20]**

Heterogeneity: Tau² = 1.39; Chi² = 14.15, df = 1 (P = 0.0002); I² = 93%
Test for overall effect: Z = 0.57 (P = 0.57)

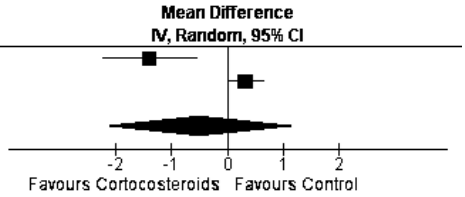


Figure 11. Adverse Events Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Cortocosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CAPE COVID 2020	28	75	30	73	6.2%	0.91 [0.61, 1.36]
COVID STEROID 2021	1	15	0	14	0.1%	2.81 [0.12, 63.83]
DEXA-COVID 19 2020	3	7	11	12	1.3%	0.47 [0.20, 1.12]
Edalatifard 2020	2	34	2	28	0.3%	0.82 [0.12, 5.48]
Ghanei 2021	47	105	101	210	15.5%	0.93 [0.72, 1.20]
REMAP-CAP 2020	9	278	1	101	0.2%	3.27 [0.42, 25.49]
Steroids-SARI 2020	23	24	23	23	76.3%	0.96 [0.86, 1.08]
Total (95% CI)		**538**		**461**	**100.0%**	**0.95 [0.86, 1.05]**
Total events	113		168			

Heterogeneity: Tau² = 0.00; Chi² = 4.58, df = 6 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)

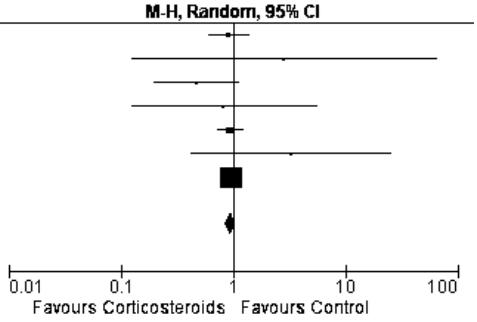


Figure 12. Nosocomial Infection Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Cortocosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CAPE COVID 2020	28	76	30	73	98.4%	0.90 [0.60, 1.34]
Edalatifard 2020	1	34	0	28	1.6%	2.49 [0.11, 58.74]
Total (95% CI)		**110**		**101**	**100.0%**	**0.91 [0.61, 1.36]**
Total events	29		30			

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)

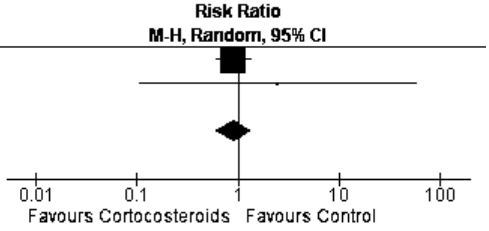


Figure 13. Gastrointestinal Symptoms Forest Plot for Type and Dosing of Corticosteroids

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Edalatifard 2020	1	32	1	16	6.1%	0.50 [0.03, 7.49]
Ghanei 2021	11	116	22	220	93.9%	0.95 [0.48, 1.89]
Total (95% CI)		**148**		**236**	**100.0%**	**0.91 [0.47, 1.78]**
Total events	12		23			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

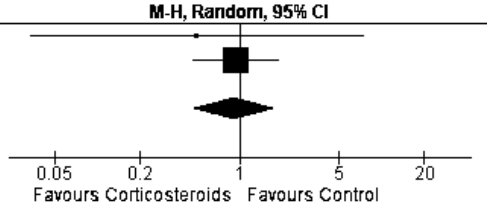


Figure 14. Mortality Forest Plot for Early versus Non-Early Initiation of Corticosteroids

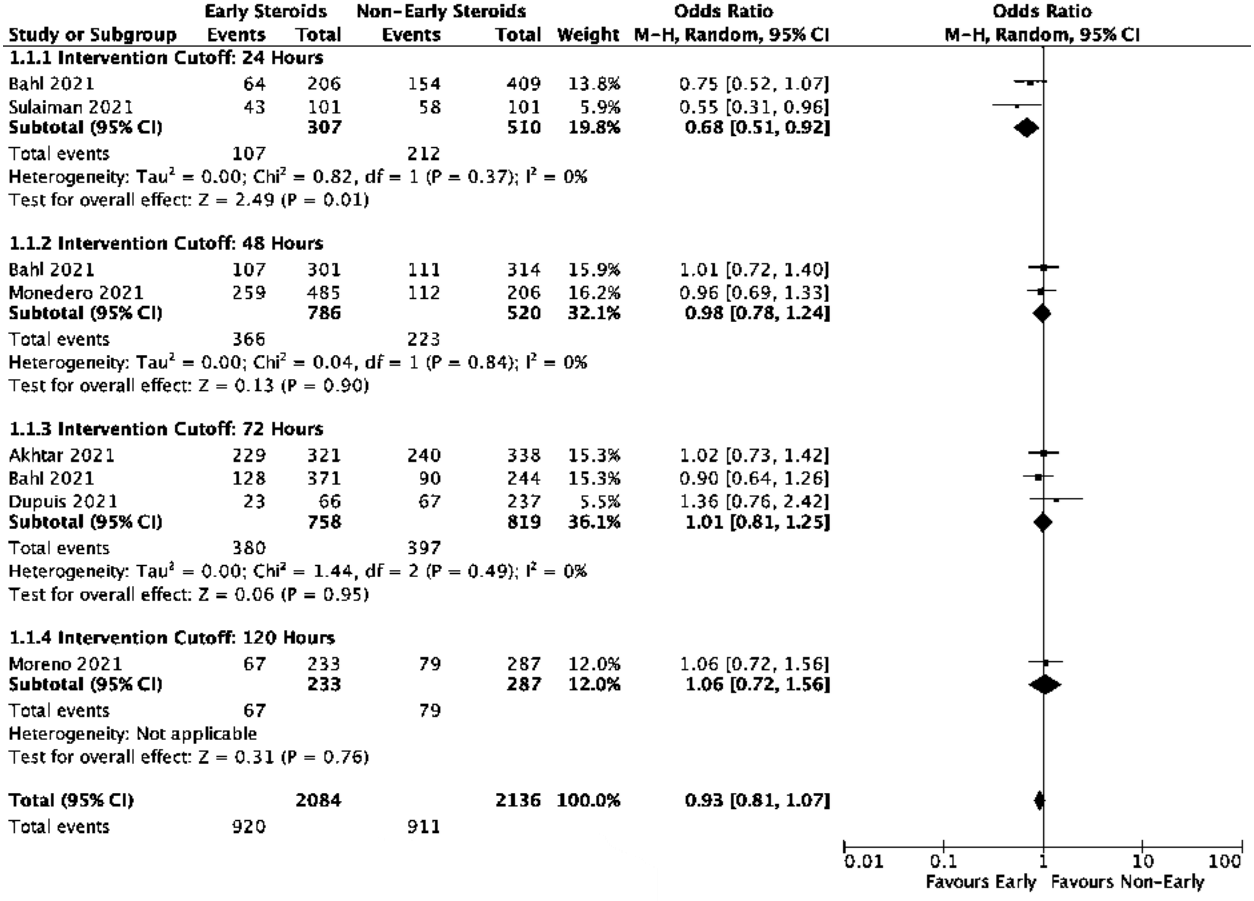


Figure 15. Need for Mechanical Ventilation Forest Plot for Early versus Non-Early Initiation of Corticosteroids

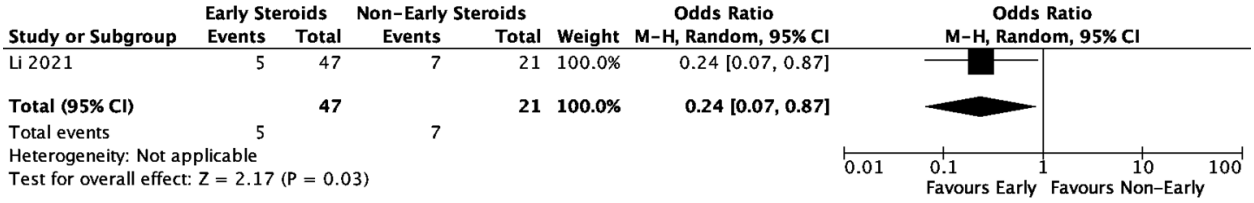


Figure 16. Adverse Events: Hyperglycemia Forest Plot for Early versus Non-Early Initiation of Corticosteroids

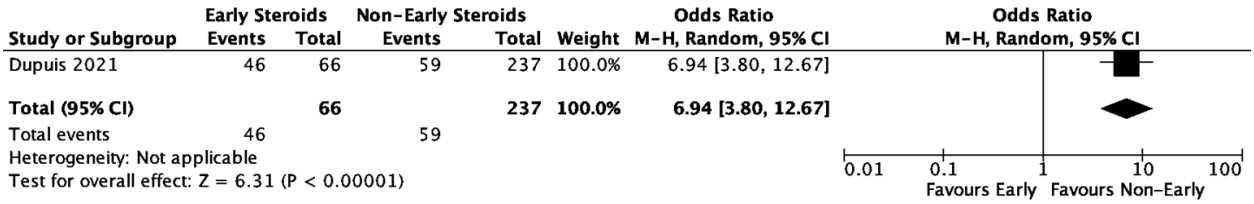


Figure 17. Adverse Events: Blood Stream Infection Forest Plot for Early versus Non-Early Initiation of Corticosteroids

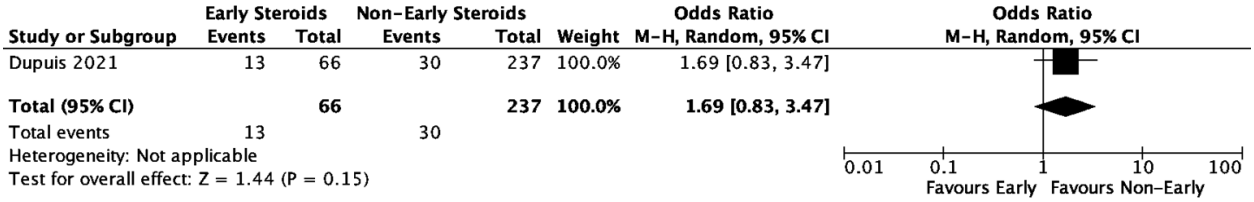
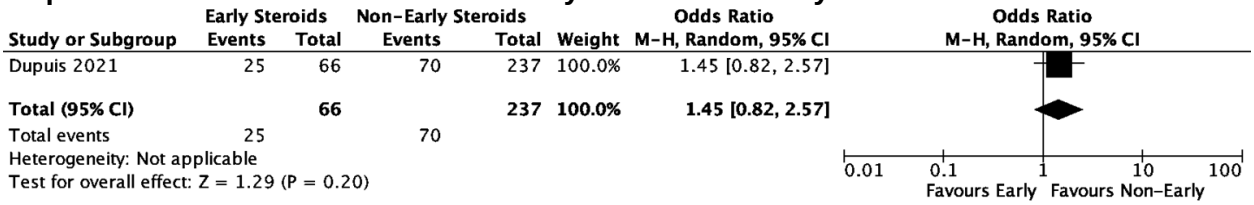


Figure 18. Adverse Events: Incidence of Hospital-acquired Pneumonia and Ventilator-acquired Pneumonia Forest Plot for Early versus Non-Early Initiation of Corticosteroids



Appendix 7. Table of Ongoing Studies

Table 8A. Characteristics of Ongoing Studies

Title (NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
Dexamethasone Vs Methylprednisolone for the Treatment of Patients with ARDS Caused by COVID-19 (NCT04499313)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	20 to 80 years old with moderate to severe COVID-19 requiring hospitalization	August 5, 2020 – ongoing recruitment Bangladesh
Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia (MEDEAS RCT) (NCT04636671)	Methylprednisolone Dexamethasone	Single-center Randomized Open-label Trial	18 years and older with COVID-19 on oxygen support, CPAP, or NPPV	April 14, 2021 – ongoing recruitment Italy
Comparison Between Prednisolone and Dexamethasone on Mortality in Patients on Oxygen Therapy, With CoViD-19 (COPreDex) (NCT04765371)	Dexamethasone Prednisolone	Multicenter Randomized Open-label Trial	18 years and older with COVID-19 requiring oxygen therapy	March 3, 2021 – October 2023 France
Glucocorticoid Therapy in Coronavirus Disease COVID-19 Patients (NCT04780581)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	18 years and older with CT-confirmed COVID-19 requiring oxygen therapy	February 1, 2021 – December 31, 2021 Spain

RCT on the Efficacy of Dexamethasone Versus Methyl Prednisolone in Covid-19 Infected Patients with High Oxygen Flow (NCT05062681)	Dexamethasone Methylprednisolone	Single-center Randomized Single-blind Trial	18 years and older with COVID-19 on high oxygen flow therapy or positive pressure ventilation	September 15, 2021 – March 15, 2022 Egypt
Effect of Two Different Doses of Dexamethasone in Patients with ARDS and COVID-19 (REMED) (NCT04663555)	Dexamethasone (20 or 6 mg/day)	Phase II Single-center Randomized Open-label Trial	18 years and older with moderate or severe COVID-19	February 2, 2021 – March 31, 2023 Czech Republic
Higher vs. Lower Doses of Dexamethasone for COVID-19 and Severe Hypoxia (COVIDSTEROID2) (NCT04509973)	Dexamethasone (12 or 6 mg/day)	Multicenter Randomized Quadruple-blind Trial	18 years and older COVID-19 patients with severe hypoxia	August 27, 2020 – November 17, 2021 Denmark India Sweden Switzerland
Randomized Open Investigation Determining Steroid Dose (ROIDS-Dose) (NCT04834375)	Dexamethasone (0.2 mg/kg/day or 6 mg/day)	Single-center Randomized Open-label Trial	18 years and older COVID-19 patients with hypoxemia	March 19, 2021 – April 19, 2022 USA
The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia (NCT04263402)	Methylprednisolone (< 40 or 40-80mg/day)	Single-center Randomized Single-blind Trial	18 years and older COVID-19 patients with severe pneumonia	February 1, 2020 – ongoing recruitment China
Efficacy of DEXamethasone in Patients with Acute Hypoxemic REspiratory Failure Caused by INfEctions (DEXA-REFINE) (NCT04545242)	Dexamethasone (6 mg/day or 20 mg/day x 5 days + 10 mg/day x 5 days)	Phase IV Multicenter Randomized Open-label Trial	18 years and older intubated and mechanically ventilated COVID-19 patients	February 8, 2021 – December 30, 2023 Spain
Timing of Corticosteroids in COVID-19 (NCT04530409)	Early-Dexamethasone Late-Dexamethasone	Phase IV Single-center Randomized Open-label Trial	18 years and older with mild or moderate severity COVID-19	February 10, 2021 – ongoing recruitment Egypt

DEXamethasone EARLY Administration in Hospitalized Patients with Covid-19 Pneumonia (EARLYDEXCoV2) (NCT04836780)	Early-Dexamethasone Late-Dexamethasone	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients with infiltrates on chest radiography or CT	June 10, 2021 – March 30, 2022 Spain
Evaluation of the Efficacy of High Doses of Methylprednisolone in SARS-CoV2 (COVID-19) Pneumonia Patients (NCT04673162)	Methylprednisolone + Dexamethasone Dexamethasone	Multicenter Randomized Quadruple-blind Trial	18 years and older with COVID-19 on non-invasive oxygen support	December 2020 (not yet recruiting) Italy
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP) (NCT02735707)	Hydrocortisone (fixed duration vs. shock-dependent)	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients admitted to an ICU for severe community acquired pneumonia	October 12, 2020 – December 2023 USA Australia Belgium Canada Croatia Germany Hungary Ireland Netherlands New Zealand Portugal Romania Spain UK

Table 8B. Characteristics of Ongoing Studies

Title (NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
Timing of Corticosteroids in COVID-19 (NCT04530409)	Early Administration of Dexamethasone given mild to moderate COVID-19 Late Administration of Dexamethasone during deterioration	Randomized Controlled Trial	Adults patients 18 years old and above with mild to moderate COVID-19	February 10, 2021 – August 15, 2021 (No results posted as of December 5, 2021) Cairo, Egypt