



## EVIDENCE SUMMARY

### RESEARCH QUESTION: Among COVID-19 patients, should intravenous corticosteroids be used in treatment?

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### RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of dexamethasone for up to 10 days among adult patients with severe and critical COVID-19.	Moderate	Strong
We suggest the use of methylprednisolone 1-2mg/kg/day for 5 to 10 days as an alternative to dexamethasone among adult patients with severe and critical COVID-19.	Very low	Weak
We suggest the use of dexamethasone at 0.15mg/kg/day or a maximum dose of 6mg per day for up to 10 days among pediatric patients with severe and critical COVID-19.	Very low	Weak
We recommend the use of standard-dose dexamethasone at 6mg to 12mg per day among adult patients with severe and critical COVID-19.	Moderate	Strong
We recommend against the use of corticosteroids among mild and moderate (non- oxygen requiring) COVID-19 patients.	Moderate	Strong
We suggest that steroid therapy be initiated as soon as diagnosed or categorized as severe and critical COVID-19.	Very low	Weak

### Consensus Issues

The available evidence still supports the recommendation of using standard dose dexamethasone for up to 10 days for adult patients with severe and critical COVID-19. In the pediatric population, there is very limited data on the use and its adverse events in COVID-19. This present recommendation was also cross referenced with the existing local guidelines from the Pediatric Infectious Disease Society of the Philippines (PIDSP).

### KEY FINDINGS

- The use of intravenous methylprednisolone when compared with intravenous dexamethasone demonstrated significant reduction in mortality, marginal clinical improvement measured using the WHO Ordinal Scale for Clinical Improvement, and reduction in inflammatory markers. However, other clinical outcomes such as need for mechanical ventilation, oxygen support escalation, and need for intensive care unit admission were all inconclusive. Overall certainty of evidence was very low.



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- The use high-dose dexamethasone (>12mg per day) when compared with the standard (6-12mg per day) dosing regimen did not show benefits in terms of all-cause mortality at 28, 60, and 90 days, need for mechanical ventilation, ventilator-free days, and incidence of serious adverse events which include secondary bacterial and fungal infection, hyperglycemia, and thrombotic events. Overall certainty of evidence was moderate.
- In terms of the timing of corticosteroid initiation, pooled data showed a trend towards reduction in mortality for early (within 24 hours of admission) initiation of corticosteroids. Incidence of mechanical ventilation was likewise reduced when corticosteroids are initiated early on admission. Overall certainty of evidence was very low.
- Safety and effectiveness of corticosteroids for COVID-19 have not been adequately evaluated in clinical trials with pediatric patients. Multivariable regression analysis in one multinational prospective cohort study in pediatric critical COVID-19 patients without multisystem inflammatory syndrome showed that the effect of dexamethasone or methylprednisolone on mortality was inconclusive. Overall certainty of evidence was very low.

## WHAT'S NEW IN THIS VERSION?

This review includes evidence updates on the use of intravenous methylprednisolone versus dexamethasone (4 new randomized controlled trials), standard-dose at 6-12mg per day versus high-dose dexamethasone at >12mg per day (6 new randomized controlled trials), and early (or within 24 hours of admission) versus non-early (more than 24 hours of admission) initiation of corticosteroids (1 new retrospective cohort study) in adult patients with severe and critical COVID-19.

Additionally, new evidence base on corticosteroid, particularly dexamethasone and methylprednisolone, use in pediatric critical COVID-19 patients without multisystem inflammatory syndrome (1 new prospective cohort study).

## PREVIOUS RECOMMENDATIONS

*As of 03 January 2022*

**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 6mg to 12mg 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.



## INTRODUCTION

Corticosteroids mitigate Coronavirus Disease-19 (COVID-19)-induced systemic inflammatory response leading to reduction in lung injury and multi-system organ dysfunction [1]. Clinical trials have demonstrated that systemic corticosteroid therapy significantly improve clinical outcomes and reduces mortality among hospitalized patients with COVID-19 who require supplemental oxygenation [1,2]. Interim findings from the RECOVERY trial first published in 2020 [3] prompted the World Health Organization to recommend the use of systemic corticosteroids, specifically dexamethasone, in hospitalized patients with severe and critical COVID-19. In the first update of the Philippine COVID-19 Living CPG as of December 2021, only dexamethasone showed significant reduction in mortality when compared to placebo in severe and critical COVID-19 patients while other systemic corticosteroids such as hydrocortisone and methylprednisolone showed a trend towards reduction of mortality. This review update aims to evaluate the efficacy and safety of (a) other systemic corticosteroids other than dexamethasone, (b) standard-dose versus high-dose dexamethasone, and (c) timing of initiation of corticosteroids.

## REVIEW METHODS

We searched PubMed, Cochrane Library, BioRxiv and MedRxiv pre-prints, 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. An updated search was performed on 23 October 2022. Detailed search strategies are presented in Appendix 2.

## RESULTS

We found 14 RCTs which compared different IV corticosteroids (dexamethasone, hydrocortisone, and methylprednisolone) with placebo [2,4-15], four RCTs which compared methylprednisolone and dexamethasone [16-19], five RCTs which compared standard versus high-dose dexamethasone [20-25], and eight cohort studies that compared early and non-early or delayed initiation of corticosteroids [26-33]. A total of 13,325 COVID-19 patients with severe and critical illness were analyzed in this review [2,4-33]. The IV corticosteroids used were dexamethasone [2,5,9,11], hydrocortisone [2,4,12], methylprednisolone [6,8,10,13,14,15], and prednisolone [7]. Duration of use for each of the IV corticosteroids were reported (Range; Mean  $\pm$  SD) as follows: dexamethasone (10 days), hydrocortisone (7-14 days; 9.33  $\pm$  3.3 days), methylprednisolone (3-10 days; 5.25  $\pm$  2.28 days), and prednisolone (5 days). Characteristics of included studies are summarized in Appendix 4.

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) [2,4-15].

### **Dexamethasone for Adult Patients with Severe and Critical COVID-19**

Compared to placebo, only dexamethasone showed statistically significant benefit in decreasing the risk of mortality (RR 0.86, 95% CI 0.79-0.94;  $I^2=0\%$ ; moderate certainty) [2,5,9,11] 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 Systemic Corticosteroids: Hydrocortisone, Methylprednisolone, and Prednisolone**

The hydrocortisone group (RR 0.85, 95% CI 0.50-1.44;  $I^2=51%$ ; moderate certainty) [2,4,12], methylprednisolone group (RR 0.82, 95% CI 0.59-1.16;  $I^2=38%$ ; moderate certainty) [6,8,10,13,14,15], and prednisolone group (RR 0.63, 95% CI 0.21-1.92; moderate certainty) [7] 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) [14]. Similarly, included studies which utilized hydrocortisone, methylprednisolone, and prednisolone did not demonstrate significant difference for a majority of the other outcomes; particularly, all-cause mortality at 28 days (HR 0.80, 95% CI 0.24-2.61; low certainty) [14], COVID-19-related mortality in 28 days (HR 0.96, 95% CI 0.24-3.84; low certainty) [14], clinical improvement in 28 days (HR 0.93, 95% CI 0.65-1.33;  $I^2=0%$ ; low certainty) [14,15], ICU admission (RR 0.78, 95% CI 0.32-1.90;  $I^2=0%$ ; low certainty) [8,15], need for endotracheal intubation (RR 0.69, 95% CI 0.40-1.18;  $I^2=0%$ ; low certainty) [6,10], eventual extracorporeal membrane oxygenation (RR 0.96, 95% CI 0.14-6.64; moderate certainty) [6], and life support-free days (MD -12.68, 95% CI -40.28 to 14.92;  $I^2=95%$ ; low certainty) [6,14]. Regarding length of hospital stay, one study showed that patients given prednisolone had significantly shorter stay when compared with placebo (MD -0.90 days, 95% CI -1.56 to -0.24; low certainty) [7]. The pooled data for length of hospital stay did not show a significant difference between the methylprednisolone and placebo (MD -0.28 days, 95% CI -1.62 to 1.07;  $I^2=93%$ ; low certainty) [10,13,15].

## **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) [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 for Non-Oxygen-Requiring Adult Patients with COVID-19**

The RECOVERY Trial [11] provided a subgroup analysis on the effect of dexamethasone on mortality among non-oxygen requiring COVID-19 patients. Result showed a trend towards increased mortality at 28 days when dexamethasone was given to COVID-19 patients who did not need oxygen therapy at randomization (RR 1.19, 95% CI 0.92-1.55; moderate certainty).

## **Other Systemic Corticosteroids: Methylprednisolone versus Dexamethasone**

Four randomized controlled trials [16-19] assessed the efficacy and safety of methylprednisolone at 1-2mg/kg/day for up to 5 to 7 days or 250mg for 3 days versus dexamethasone 6mg per day for up to 10 days in 686 patients with severe and critical COVID-19. A total of 359 patients were randomized to methylprednisolone while 327 patients were randomized to dexamethasone. Significant benefit for all-cause mortality at 28 days was found with the use of methylprednisolone (RR 0.37, 95% CI 0.24-0.58,  $I^2=37%$ ; moderate certainty) [16-19] while the need for mechanical ventilation (RR 1.04, 95% CI 0.41-2.65,  $I^2=69%$ ; very low certainty) [16,18-19], oxygen support escalation (RR 0.78, 95% CI 0.59-1.03,  $I^2=0%$ ; low certainty) [18-19], need for intensive care unit admission (RR 1.09, 95% CI 0.48-2.51; very low certainty) [19] were all inconclusive. Significant benefits were also found in terms of clinical improvement at 5 days (MD -1.2 points, 95% CI -1.19 to -0.48; low certainty) and 7 days (MD -1.9 points, 95% CI -2.8 to -0.79; low certainty) assessed using the WHO Ordinal Scale [16], and improvement in inflammatory markers which include C-reactive protein (MD -50.6 mg/dL, 95% CI -55.3 to -45.85;  $I^2=0%$ ; low certainty) [17,18], neutrophil-to-lymphocyte ratio (MD -6.97, 95% CI -12.1 to -1.84;  $I^2=98%$ ; low certainty) [17,18], interleukin-6 (MD -22.9 pg/mL, 95% CI -26.4 to -19.38; low certainty) [18], serum ferritin (MD -56.3 ug/L, 95% CI -99.93 to -12.67; low certainty) [17], and d-dimer levels (MD -1.1 ug/L, 95% CI -1.35 to -0.85; low certainty) [17]. With regard to adverse events, infection (RR 0.86, 95% CI 0.33-2.33; very low certainty) [19] and observed psychosis (RR 2.95, 95% CI 0.12-71.13; very low certainty) [19] were inconclusive. Development of hyperglycemia was significantly observed in the methylprednisolone arm (RR 3.35, 95% CI 1.32-8.51; low certainty) [19] when compared to dexamethasone.



## Dosing of Corticosteroid: Standard versus High-dose Dexamethasone

Six randomized controlled trials [20-25] assessed the efficacy and safety of standard-dose at 6-12mg versus high-dose at 16-24mg intravenous dexamethasone in 2,052 patients with severe and critical COVID-19. In this population, 517 out of 2,052 patients (25%) were mechanically ventilated at the start of the trials. A total of 1,007 patients were randomized to standard-dose while 1,045 patients were randomized to high-dose dexamethasone treatment arms. In these trials standard-dose intravenous dexamethasone at 6-12mg per day was compared with high-dose intravenous dexamethasone at 16-24mg per day. The effect of high-dose dexamethasone on all-cause mortality was inconclusive at 28 days (RR 0.97, 95% CI 0.81-1.15,  $I^2=30\%$ ; moderate certainty) [20-23,25], 60 days (RR 1.20, 95% CI 0.69-2.10,  $I^2=0\%$ ; moderate certainty) [21,23,24], and 90 days (RR 0.90, 95% CI 0.74-1.09,  $I^2=0\%$ ; moderate certainty) [20,22] after randomization. The risk for mechanical ventilation (RR 1.39, 95% CI 0.69-2.80,  $I^2=0\%$ ; moderate certainty) [23,24] and ventilator-free days at 28 days (MD 0.11 day, 95% CI -0.47 to 0.69; moderate certainty) [20,21] were likewise inconclusive. In terms of adverse events, risk of developing secondary bacterial or fungal infection, and hospital-associated infections (RR 0.89; 95% CI 0.63-1.24,  $I^2=0\%$ , moderate certainty) [20,21,23-25], risk of hyperglycemia requiring insulin therapy (RR 1.10, 0.86-1.41;  $I^2=0\%$ , moderate certainty) [23-25], and risk of any thrombotic event (RR 0.39, 0.05-3.22;  $I^2=26\%$ , moderate certainty) [23-24] were inconclusive as well.

## Timing of Administration of Corticosteroids

Eight retrospective cohort studies [26-33] 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. Three studies [26-28] provided data for  $\leq 24$  hours versus  $>24$  hours, two studies [26,29] provided data for  $\leq 48$  hours versus  $>48$  hours, three studies [26,30,31] provided data for  $\leq 72$  versus  $>72$  hours, and one study [32] provided data for  $\leq 120$  hours versus  $>120$  hours. A trend towards benefit was observed 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 0.82, 95% CI 0.53-1.25;  $I^2=67\%$ ; very low certainty) [26-28]. 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) [26,29], 72 hours (OR 1.01, 95% CI 0.81-1.25;  $I^2=0\%$ ; low certainty) [26,30,31], and 120 hours (OR 1.06, 95% CI 0.72-1.56; very low certainty) [32] from admission, mortality benefit became largely inconclusive. Use of mechanical ventilation was significantly reduced when systemic corticosteroids were initiated within 24 hours of admission (OR 0.24, 95% CI 0.07-0.87; low certainty) [33]. 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-associated or ventilator-associated pneumonia (OR 1.31, 1.00-1.71;  $I^2=0\%$ ; low certainty) [28,31].

## Corticosteroids for Pediatric Patients with Severe and Critical COVID-19

One multinational prospective cohort study [34] described the clinical profiles and outcomes, and evaluated factors associated with mortality in children with critical COVID-19. The study population included 557 critically ill pediatric patients (median age = 8 years; IQR 2-12.4) hospitalized for COVID-19 in 18 countries throughout North America, Latin America, and Europe from 01 April to 31 December 2020. Overall hospital mortality was 10%. Multivariable regression analysis showed that the effect of dexamethasone (OR 0.97; 95% CI 0.49-1.91) or methylprednisolone (OR 0.93; 95% CI 0.43-2.03) on mortality was inconclusive. Odds ratio for mortality was adjusted for sex, age  $<2$  years, region, and Pediatric Risk of Mortality III (PRISM III). No data on other clinically important outcomes such as need for mechanical intubation, oxygen support escalation, need for intensive care unit admission, clinical improvement or deterioration, and adverse events relative to corticosteroid use were presented in the study.



## Certainty of evidence

### **Corticosteroids in Severe to Critical COVID-19**

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 [11] included patients who were given oral dexamethasone. 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 5). Seven RCTs were either open-label trials or did not blind the personnel and the outcome assessors [4,7-9,12-15]. Data of two RCTs were extracted from the WHO REACT group evidence review as their full articles could not be retrieved [2]. Certain outcomes, namely all-cause mortality (in hydrocortisone group) [2,4,12], 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.

### **Dexamethasone in Mild to Moderate COVID-19**

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 [11].

### **Dexamethasone versus Methylprednisolone**

Overall certainty of evidence for the use of methylprednisolone when compared to dexamethasone was very low because of serious risk of bias involving selective reporting bias in two studies [16,17] which excluded patients who developed adverse events in the final analysis (censored analysis), significant heterogeneity, and imprecision of results in some of the outcomes.

### **Standard-dose (6-12mg) versus High-dose (16-24mg) Dexamethasone**

In terms of standard and high-dose dexamethasone, certainty of evidence was downgraded to moderate certainty due to imprecision [20-25].

### **Early versus Non-Early Initiation of Corticosteroids**

Cohort studies [26-33] 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 [31,32]. As of 05 December 2021, no randomized controlled trial is currently available on this clinical question.

### **Corticosteroids for Pediatric Patients with Severe and Critical COVID-19**

Overall certainty of evidence on the use of corticosteroids, particularly dexamethasone and methylprednisolone, was very low due to imprecision [34].

## RECOMMENDATIONS FROM OTHER GROUPS

At present, the WHO [41], US National Institutes of Health [1], Infectious Diseases Society of America [42], UK National Institute for Health and Care Excellence [43], Australian Guidelines for Clinical Care of People with COVID-19 [44], Japanese Living Recommendations on Drug Management for COVID-19 [45], and the Singapore National Centre for Infectious Diseases [46] continue to recommend the use of dexamethasone at 6mg per day for up to 10 days for adult patients with severe and critical COVID-19. Furthermore, in the absence of dexamethasone, total daily equivalent systemic corticosteroids such as methylprednisolone, hydrocortisone, and prednisone may be used.

The WHO [41], US National Institutes of Health [1], UK National Institute for Health and Care Excellence [43], Australian Guidelines for Clinical Care of People with COVID-19 [44], and the Singapore National Centre for Infectious Diseases [46], likewise recommended the use of systemic corticosteroids, particularly dexamethasone, in the pediatric population. Dosing recommendations from other groups for dexamethasone at 0.15mg per kg per day or a maximum of 6mg per day for up to 6 days were based on RECOVERY Trial protocol.



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## ONGOING STUDIES AND RESEARCH GAPS

As of 23 October 2022, there are two completed (no posted results yet) and one ongoing trials on methylprednisolone versus dexamethasone (n=850 patients), one ongoing trial on standard versus high-dose dexamethasone (n=200 patients), and two completed (no posted results yet) and one ongoing trials on timing (early versus delayed) corticosteroids (n=1,052 patients).

## ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

### COST, PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

From our literature search, one cost-effectiveness analysis on the use of dexamethasone (6mg oral or IV) was found. A study done in South Africa shows that even though there was a cost increase with the addition of dexamethasone to standard care, its cost still fell below willingness to pay thresholds and approaches 100% cost-effectiveness for thresholds beyond US\$500 [35]. 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) [35,36].

**Table 1. IV Corticosteroid Prices based on The Philippine Drug Price Reference Index [37,39]**

Drug	Sample Regimen	Unit Price	Price/Regimen
Dexamethasone	20mg/day x 5 days + 10mg/day x 5 days	₱40 to ₱135 per 5mg vial	₱800 to ₱2,700
Methylprednisolone	40mg BID x 3 days + 20mg TID x 3 days	₱300 to ₱690 per 40mg vial	₱3,000 to ₱20,700*

\* Computed for a 70kg patient for a 5 to 10-day methylprednisolone therapy

Intravenous corticosteroids are some of the most readily available drugs globally [37]. The WHO has listed dexamethasone and prednisolone as essential medicines while in the Philippines, dexamethasone, hydrocortisone, methylprednisolone, and prednisolone are similarly recognized in the national formulary [38,39]. These drugs were deemed highly acceptable by the WHO due to their ease of administration, relatively short courses, and generally benign safety profile [38].



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## Appendix 1: Preliminary Evidence to Decision

**Table 1. Summary of initial judgements prior to the panel discussion (N=8/10)**

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
	No	Yes (8)	Small	Trivial (1)	Uncertain	
<b>Problem</b>	No	Yes (8)				Yes. COVID-19 patients are at risk for ICU admission. IV corticosteroids are staple critical care medications that are easily accessible.
<b>Benefits</b>	Large (1)	Moderate (6)	Small	Trivial (1)	Uncertain	<p><b>Type of Corticosteroids</b> IV corticosteroids, specifically Dexamethasone, significantly decreased all-cause mortality in COVID-19 patients. <b>Compared to placebo – Adults RR 0.86, 95% CI 0.79-0.94; I<sup>2</sup>=0%; Moderate Certainty, compared to Methylprednisolone RR 0.37, 95% CI 0.24-0.58, I<sup>2</sup> Moderate Certainty; Children OR 0.97, 95% CI 0.49-1.91</b></p> <p><b>Standard versus High-dose Dexamethasone</b> The use of high-dose dexamethasone did not further reduce all-cause mortality at 28, 60, and 90 days – <b>RR 0.97, 95% CI 0.81-1.15; RR 1.20, 95% CI 0.60-2.10; RR 0.90, 95% CI 0.74-1.09, respectively, with Moderate Certainty</b></p>



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<b>Harm</b>	Large	Moderate (5)	Small (3)	Trivial	Uncertain	<p><b>Type and Dosing of Corticosteroids</b>            Adverse events are comparable between the IV corticosteroid group and the control group as well as between the different doses of Dexamethasone.  <b>Overall RR 0.95, 95% CI 0.86-1.05; I<sup>2</sup>=0%; Low Certainty</b>  <b>Infection RR 0.86, 95% CI 0.33-2.33, Very Low Certainty</b>  <b>Hyperglycemia RR 3.35, 95% CI 1.32-8.51, Low Certainty</b>  <b>Psychosis RR 2.95, 95% CI 0.12-71.13, Very Low Certainty</b></p> <p><b>Timing of Corticosteroids</b>            Incidence of hyperglycemia was significantly found in early initiation of corticosteroids, less than 72 hours (<b>OR 6.94, 95% CI 3.80-12.67; Low Certainty</b>). Development of blood stream infection, hospital-acquired pneumonia, and ventilator-acquired pneumonia were comparable between early and later initiation of corticosteroids.</p> <p><b>Standard versus High-dose Dexamethasone</b>            No incremental harm was observed with the use of high-dose dexamethasone when compared with standard-dose:  <b>Infection RR 0.89, 95% CI 0.63-1.24, I<sup>2</sup>=0%</b>  <b>Hyperglycemia RR 1.10, 95% CI 0.86-1.41, I<sup>2</sup>=0%</b>  <b>Thrombotic events RR 0.39, 95% CI 0.05-3.22, I<sup>2</sup>=26%</b>  <b>Moderate Certainty</b></p>
		Certainty of Evidence	High			Moderate (3)



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<p><b>Balance of effects</b></p>	<p>Favors treatment (2)</p>	<p>Probably favors treatment (6)</p>	<p>Does not favor treatment or no treatment</p>	<p>Probably favors no treatment</p>	<p>Favors no treatment</p>	<p>Varies</p>	<p><b>Type and Dosing of Corticosteroids</b>            Favors IV Corticosteroids: All-cause Mortality, All-cause Mortality (Dexamethasone Group), Ventilator-free Days, WHO Ordinal Scale            Favors Dexamethasone 12mg: Ventilator-free Days, Cardiovascular Support-free Days, Renal Replacement Therapy-free Days            Favors Control: Length of ICU Stay</p> <p><b>Standard versus High-dose Dexamethasone</b>            Probably favors standard-dose dexamethasone (6-12mg/day)</p> <p><b>Timing of Corticosteroids</b>            A trend towards benefit was observed 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 (<b>OR 0.82, 95% CI 0.53-1.25; I<sup>2</sup>=67%; Very Low Certainty</b>). As initiation of systemic corticosteroids was further delayed at 48 hours (<b>OR 0.98, 95% CI 0.78-1.24; I<sup>2</sup>=0%; Low Certainty</b>), 72 hours (<b>OR 1.01, 95% CI 0.81-1.25; I<sup>2</sup>=0%; Low Certainty</b>), and 120 hours (<b>OR 1.06, 95% CI 0.72-1.56; Very Low Certainty</b>) from admission, mortality benefit became largely inconclusive. Use of mechanical ventilation was significantly reduced when systemic corticosteroids were initiated within 24 hours of admission (<b>OR 0.24, 95% CI 0.07-0.87; Low Certainty</b>).</p> <p>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-associated or ventilator-associated pneumonia (OR 1.31, 1.00-1.71; I<sup>2</sup>=0%; Low Certainty).</p>
<p><b>Values</b></p>	<p>Important uncertainty or variability (2)</p>	<p>Possibly important uncertainty or variability (3)</p>	<p>Possibly NO important uncertainty or variability (3)</p>	<p>No important uncertainty or variability</p>			<p>N/A</p>



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Resources Required	Uncertain	Large cost	Moderate cost (3)	Negligible costs or savings (3)	Moderate savings (2)	Large savings	IV Corticosteroids are relatively affordable and easily accessible in most government hospitals.
<b>Certainty of evidence of required resources</b>	No included studies	Very low	Low (3)	Moderate (5)	High		<p>Moderate</p> <p>The cost-effectiveness analysis was done in a developed western country (South Africa) using their local currency converted into US dollars. The included population had high willingness-to-pay thresholds (\$3,015 per disability-adjusted life years).</p> <p>The drug prices were lifted from the Philippine Drug Price Reference Index (last updated July 2020).</p> <p><b>Dexamethasone 6mg/day for 10 days – ₱800 to ₱2,700</b></p>
<b>Cost effectiveness</b>	No included studies	Favors the comparison	Probably favors the comparison (1)	Does not favor either the intervention or the comparison	Probably favors the intervention (3)	Favors the intervention (4)	The cost-effectiveness analysis favors the addition of dexamethasone to standard care.
<b>Equity</b>	Uncertain	Reduced	Probably reduced (1)	Probably no impact (3)	Probably increased (3)	Increased (1)	In the Philippines, dexamethasone, hydrocortisone, methylprednisolone, and prednisolone are recognized in the national formulary as essential medications. They are relatively affordable and widely accessible.
<b>Acceptability</b>	Uncertain	Varies	No	Probably no	Probably yes (4)	Yes (4)	N/A
<b>Feasibility</b>	Uncertain	Varies	No	Probably no	Probably yes (3)	Yes (5)	N/A





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## Appendix 2: Search Strategy & Results

**Table 2A. 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	<b>20,339</b>



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**Table 2B. Search Yield for Methylprednisolone versus Dexamethasone**

Search number	Search Details	Results
4	(("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms]))) AND ("steroids"[MeSH Terms] OR "glucocorticoids"[MeSH Terms] OR "dexamethasone"[Title/Abstract] OR "dex"[Title/Abstract] OR "steroid"[Title/Abstract] OR "corticosteroid"[Title/Abstract] OR "steroid"[All Fields] OR "glucocorticoid"[All Fields] OR "corticosteroid"[All Fields] OR "methylprednisolone"[Title/Abstract] OR "methylprednisolone"[All Fields] OR "methylpred"[Title/Abstract]) AND ("COVID"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "sars coronavirus 2"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019 novel cov"[Title/Abstract] OR "ncov 2019"[Title/Abstract] OR "ncov 19"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "novel coronavirus disease"[Title/Abstract] OR ("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND "coronavirus virus disease"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "corona virus disease 2019"[Title/Abstract] OR "novel coronavirus pneumonia"[Title/Abstract] OR "novel corona virus pneumonia"[Title/Abstract])	776
3	"COVID"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "sars coronavirus 2"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019 novel cov"[Title/Abstract] OR "ncov 2019"[Title/Abstract] OR "ncov 19"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "novel coronavirus disease"[Title/Abstract] OR ("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND "coronavirus virus disease"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "corona virus disease 2019"[Title/Abstract] OR "novel coronavirus pneumonia"[Title/Abstract] OR "novel corona virus pneumonia"[Title/Abstract]	292,898
2	"steroids"[MeSH Terms] OR "glucocorticoids"[MeSH Terms] OR "dexamethasone"[Title/Abstract] OR "dex"[Title/Abstract] OR "steroid"[Title/Abstract] OR "corticosteroid"[Title/Abstract] OR "steroid"[All Fields] OR "glucocorticoid"[All Fields] OR "corticosteroid"[All Fields] OR "methylprednisolone"[Title/Abstract] OR "methylprednisolone"[All Fields] OR "methylpred"[Title/Abstract]	1,298,629
1	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms]))	1,454,148



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**Table 2C. Search Yield for High-dose versus Standard-dose Dexamethasone**  
(Updated as of 10 October 2022)

Search number	Query	Search Details	Results
44	#13 and #23 and #43	((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms]))) AND ("steroids"[MeSH Terms] OR "glucocorticoids"[MeSH Terms] OR "dexamethasone"[Title/Abstract] OR "dex"[Title/Abstract] OR "steroid"[Title/Abstract] OR "corticosteroid"[Title/Abstract] OR "steroid"[All Fields] OR "glucocorticoid"[All Fields] OR "corticosteroid"[All Fields]) AND ("COVID"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "sars coronavirus 2"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019 novel cov"[Title/Abstract] OR "ncov 2019"[Title/Abstract] OR "ncov 19"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "novel coronavirus disease"[Title/Abstract] OR ("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND "coronavirus virus disease"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "corona virus disease 2019"[Title/Abstract] OR "novel coronavirus pneumonia"[Title/Abstract] OR "novel corona virus pneumonia"[Title/Abstract])	591
43	#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42	"COVID"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "sars coronavirus 2"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019 novel cov"[Title/Abstract] OR "ncov 2019"[Title/Abstract] OR "ncov 19"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "novel coronavirus disease"[Title/Abstract] OR ("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND "coronavirus virus disease"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "corona virus disease 2019"[Title/Abstract] OR "novel coronavirus pneumonia"[Title/Abstract] OR "novel corona virus pneumonia"[Title/Abstract]	224,063
42	novel corona virus pneumonia [tiab]	"novel corona virus pneumonia"[Title/Abstract]	5
41	novel coronavirus pneumonia [tiab]	"novel coronavirus pneumonia"[Title/Abstract]	535
40	corona virus disease 2019 [tiab]	"corona virus disease 2019"[Title/Abstract]	844
39	coronavirus disease 2019 [tiab]	"coronavirus disease 2019"[Title/Abstract]	39,950
38	novel coronavirus virus disease [tiab]	("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND "coronavirus virus disease"[Title/Abstract]	1
37	novel coronavirus disease [tiab]	"novel coronavirus disease"[Title/Abstract]	3,095
36	severe acute respiratory syndrome coronavirus 2 [tiab]	"severe acute respiratory syndrome coronavirus 2"[Title/Abstract]	22,601
35	nCoV 19 [tiab]	"ncov 19"[Title/Abstract]	522
34	nCoV 2019 [tiab]	"ncov 2019"[Title/Abstract]	63
33	2019-novel CoV [tiab]	"2019 novel cov"[Title/Abstract]	7
32	2019nCoV [tiab]	"2019nCoV"[Title/Abstract]	1,327



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31	2019 nCoV [tiab]	"2019 ncov"[Title/Abstract]	1,895
30	SARS coronavirus 2 [tiab]	"sars coronavirus 2"[Title/Abstract]	353
<b>Search number</b>	<b>Query</b>	<b>Search Details</b>	<b>Results</b>
29	SARSCoV-2 [tiab]	"SARSCoV-2"[Title/Abstract]	265
28	SARS-CoV2 [tiab]	"SARS-CoV2"[Title/Abstract]	3,050
27	SARS-CoV-2 [tiab]	"SARS-CoV-2"[Title/Abstract]	75,466
26	COVID19 [tiab]	"COVID19"[Title/Abstract]	191,063
25	COVID-19 [tiab]	"COVID-19"[Title/Abstract]	201,194
24	COVID [tiab]	"COVID"[Title/Abstract]	203,689
23	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	"steroids"[MeSH Terms] OR "glucocorticoids"[MeSH Terms] OR "dexamethasone"[Title/Abstract] OR "dex"[Title/Abstract] OR "steroid"[Title/Abstract] OR "corticosteroid"[Title/Abstract] OR "steroid"[All Fields] OR "glucocorticoid"[All Fields] OR "corticosteroid"[All Fields]	1,266,641
22	corticosteroid*	"corticosteroid"[All Fields]	114,548
21	glucocorticoid*	"glucocorticoid"[All Fields]	242,706
20	steroid*	"steroid"[All Fields]	397,459
19	corticosteroid [tiab]	"corticosteroid"[Title/Abstract]	53,614
18	steroid [tiab]	"steroid"[Title/Abstract]	143,288
17	dex* [tiab]	"dex"[Title/Abstract]	11,236
16	dexamethasone [tiab]	"dexamethasone"[Title/Abstract]	61,590
15	glucocorticoids [mesh]	"glucocorticoids"[MeSH Terms]	68,413
14	steroids [mesh]	"steroids"[MeSH Terms]	892,683
13	#8 not #12	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms]))	1,406,743
12	#9 not #11	"animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms])	4,963,911
11	#9 and #10	"animals"[MeSH Terms] AND "humans"[MeSH Terms]	20,203,095
10	humans [mh]	"humans"[MeSH Terms]	20,203,095
9	animals [mh]	"animals"[MeSH Terms]	25,167,006
8	#1 or #2 or #3 or #4 or #5 or #6 or #7	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]	1,521,766
7	trial [ti]	"trial"[Title]	257,229
6	randomly [tiab]	"randomly"[Title/Abstract]	377,680
5	clinical trial as topic [mesh: noexp]	"clinical trials as topic"[MeSH Terms]	370,828
4	placebo [tiab]	"placebo"[Title/Abstract]	232,322
3	randomized [tiab]	"randomized"[Title/Abstract]	600,746



# Philippine COVID-19 Living Clinical Practice Guidelines

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2	controlled clinical trial [pt]	"controlled clinical trial"[Publication Type]	650,791
1	randomized controlled trial [pt]	"randomized controlled trial"[Publication Type]	560,971



## Philippine COVID-19 Living Clinical Practice Guidelines

**Table 2D. Search Yield for Timing of Corticosteroids**

Search	Query	Results
#6	Search: <b>((corticosteroids) AND (COVID-19)) AND ((early) OR (timing))</b> ("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]))	<u>424</u>
#5	Search: <b>(early) OR (timing)</b> "early"[All Fields] OR "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	<u>1,909,206</u>
#4	Search: <b>timing</b> "timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]	<u>226,302</u>
#3	Search: <b>early</b> "early"[All Fields]	<u>1,730,924</u>
#2	Search: <b>COVID-19</b> "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])	<u>202,271</u>
#1	Search: <b>corticosteroids</b> "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]	<u>364,476</u>



## Philippine COVID-19 Living Clinical Practice Guidelines

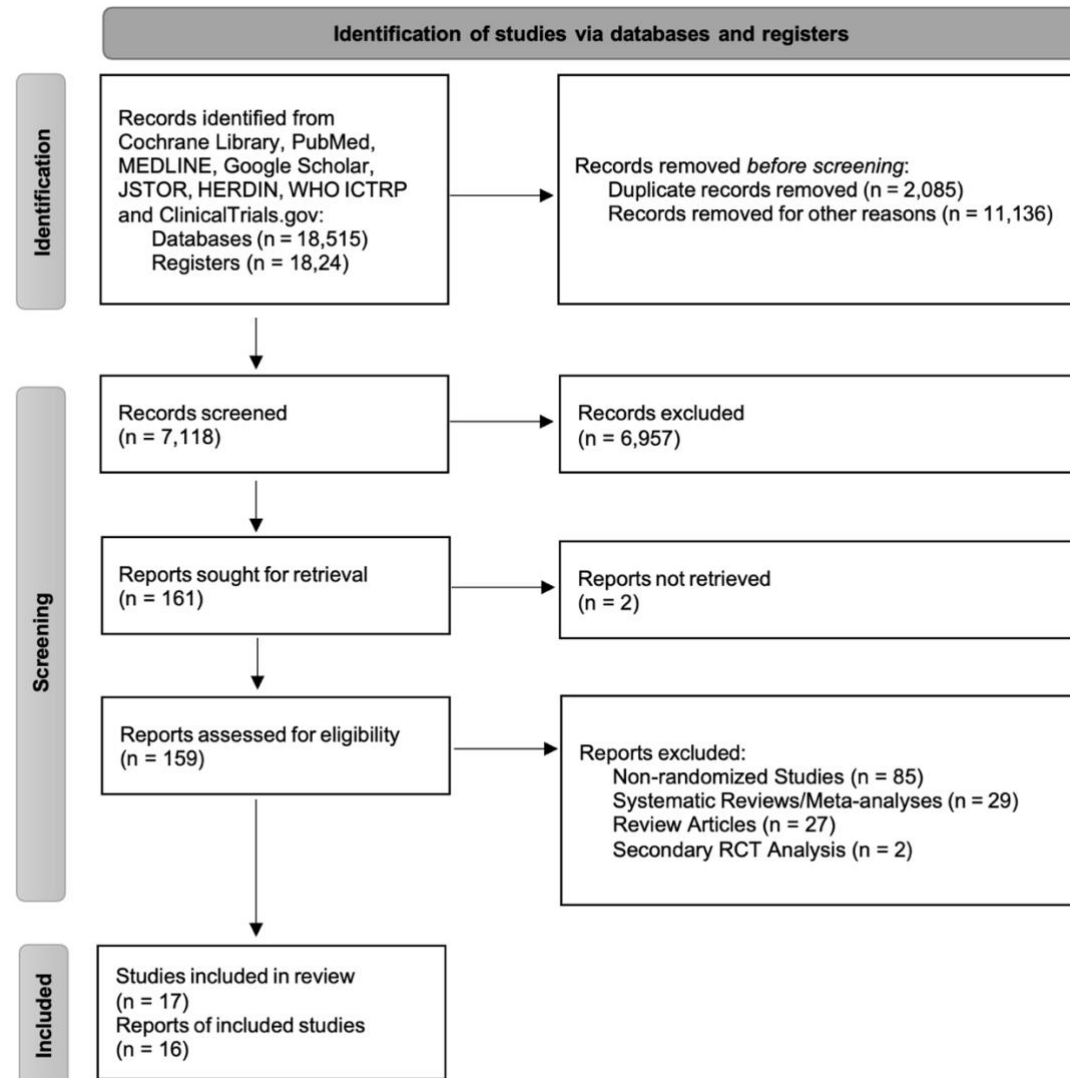
**Table 2E. Search Yield for Timing of Corticosteroids**

Search	Query	Results
3	<p>Search: ("pediatric covid 19"[Title/Abstract] OR "pediatric severe covid 19"[Title/Abstract] OR "pediatric covid 19"[Title/Abstract] OR "paediatric covid 19"[Title/Abstract] OR (("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND "severe covid 19"[Title/Abstract]) OR "paediatric covid 19"[Title/Abstract]) AND ("outcome"[All Fields] OR "outcomes"[All Fields] OR "mortality"[Title/Abstract] OR "intensive care unit"[Title/Abstract])</p> <p>("pediatric covid 19"[Title/Abstract] OR "pediatric severe covid 19"[Title/Abstract] OR "pediatric covid 19"[Title/Abstract] OR "paediatric covid 19"[Title/Abstract] OR (("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND "severe covid 19"[Title/Abstract]) OR "paediatric covid 19"[Title/Abstract]) AND ("outcome"[All Fields] OR "outcomes"[All Fields] OR "mortality"[Title/Abstract] OR "intensive care unit"[Title/Abstract])</p>	641
2	<p>Search: "outcome"[All Fields] OR "outcomes"[All Fields] OR "mortality"[Title/Abstract] OR "intensive care unit"[Title/Abstract]</p> <p>"outcome"[All Fields] OR "outcomes"[All Fields] OR "mortality"[Title/Abstract] OR "intensive care unit"[Title/Abstract]</p>	3,696,331
1	<p>Search: "pediatric covid 19"[Title/Abstract] OR "pediatric severe covid 19"[Title/Abstract] OR "pediatric covid 19"[Title/Abstract] OR "paediatric covid 19"[Title/Abstract] OR (("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND "severe covid 19"[Title/Abstract]) OR "paediatric covid 19"[Title/Abstract]</p> <p>"pediatric covid 19"[Title/Abstract] OR "pediatric severe covid 19"[Title/Abstract] OR "pediatric covid 19"[Title/Abstract] OR "paediatric covid 19"[Title/Abstract] OR (("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND "severe covid 19"[Title/Abstract]) OR "paediatric covid 19"[Title/Abstract]</p>	1,430



# Philippine COVID-19 Living Clinical Practice Guidelines

## Appendix 3: PRISMA Flow Diagrams



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





# Philippine COVID-19 Living Clinical Practice Guidelines

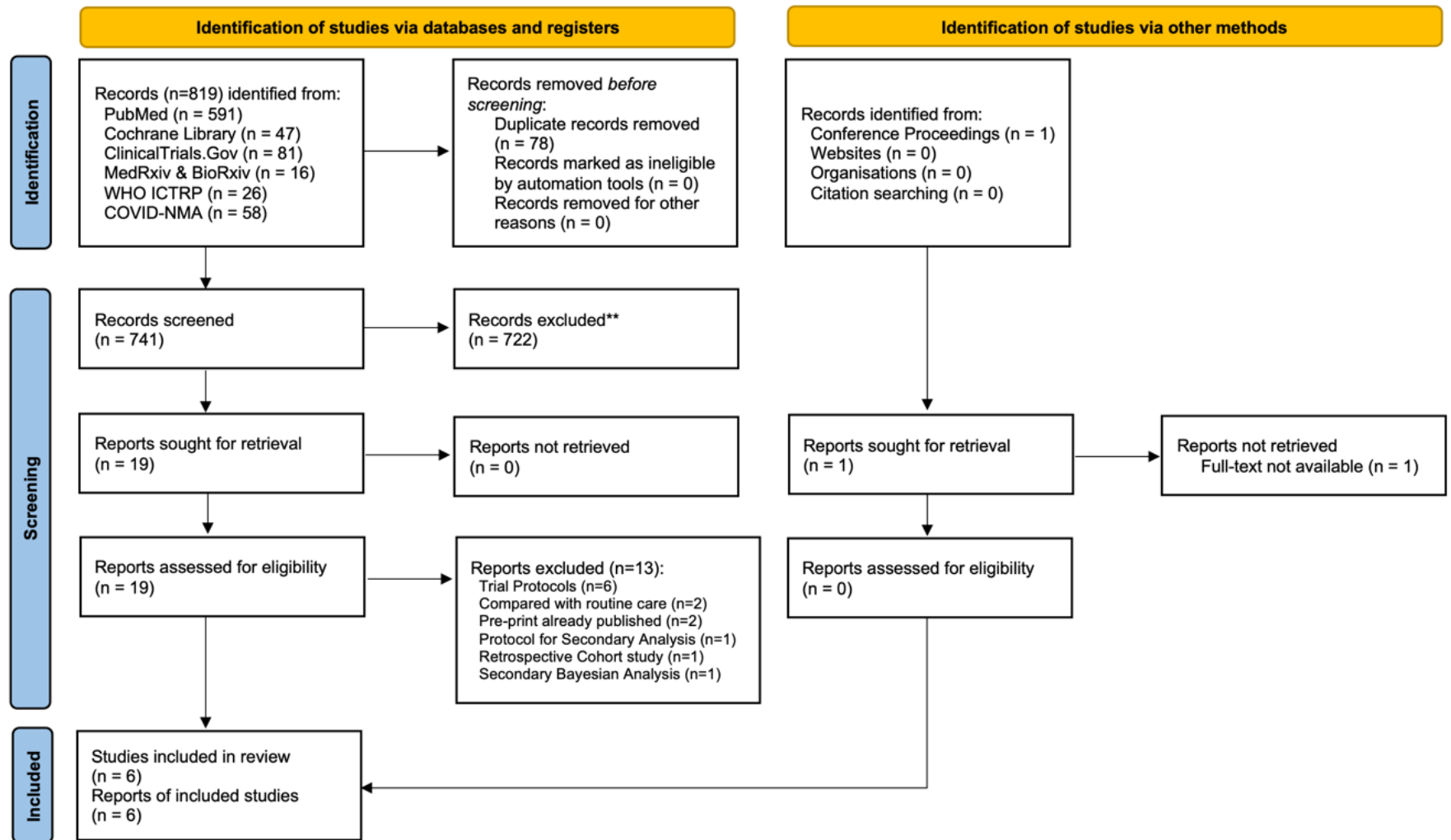
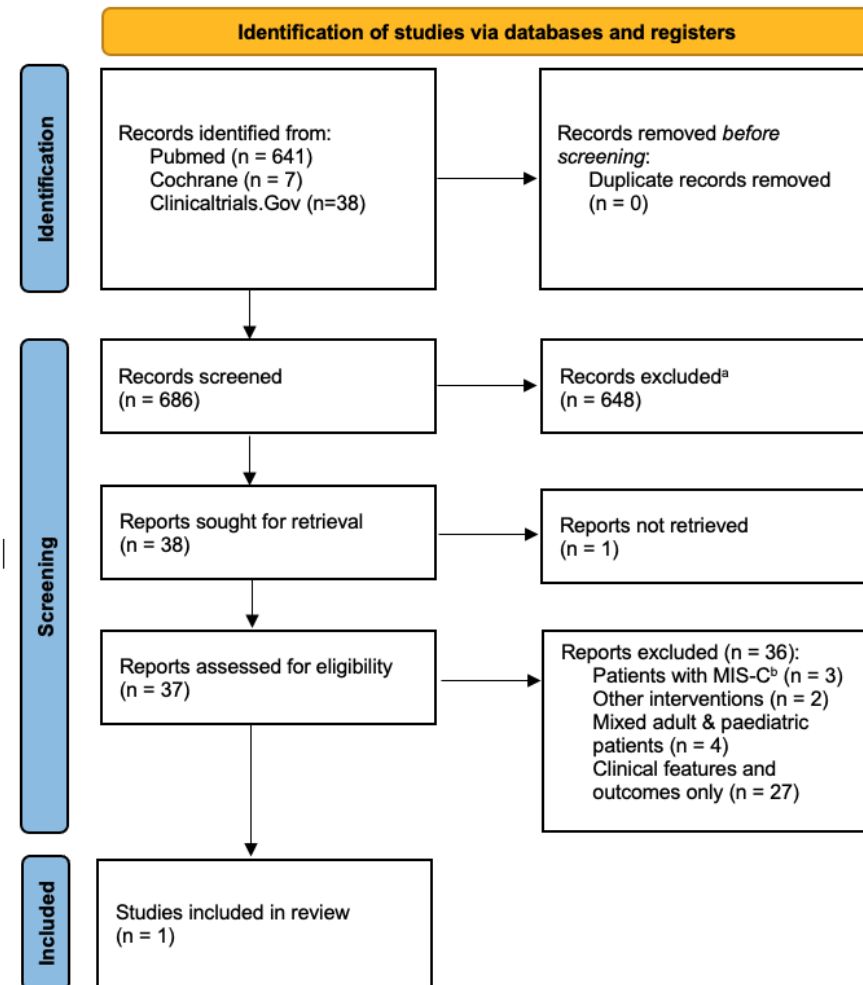


Figure 1B. PRISMA Flow Diagram for High-dose versus Standard-dose Dexamethasone



# Philippine COVID-19 Living Clinical Practice Guidelines



<sup>a</sup>Articles with indirect population (severe and critical adult COVID-19 patients) and/or interventions (mixed interventions including only corticosteroids or no comparison of corticosteroid versus no corticosteroid use)

<sup>b</sup>Multisystem inflammatory syndrome in children

**Figure 1C.** PRISMA Flow Diagram for Corticosteroids for Pediatric COVID-19



# Philippine COVID-19 Living Clinical Practice Guidelines

## Appendix 4: Characteristics of Included Studies

**Table 3A. Characteristics of Included Studies for Hydrocortisone, Dexamethasone, Prednisolone, Methylprednisolone**

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
DEXA-COVID 19 2020	COVID-19 patients with moderate to severe ARDS (n = 19)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	All-cause Mortality, Adverse Events	Multicenter Randomized Open-label Trial



## Philippine COVID-19 Living Clinical Practice Guidelines

Study ID	Patients (n)	Interventions	Outcomes	Method
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



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Study ID	Patients (n)	Interventions	Outcomes	Method
REMAP-CAP 2020	patients with severe COVID-19 (n = 379)	Hydrocortisone Fixed 7-day Course (50 mg or 100 mg every 6 hours)  Hydrocortisone Shock-Dependent Course (50 mg or 100 mg every 6 hours when in shock)	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Open-label Trial
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 x 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



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**Table 3B. Characteristics of Included Studies for Methylprednisolone versus Dexamethasone**

Study ID	Patients (n)	Interventions	Outcomes	Method
Corral-Gudino 2022	Severe and critical COVID-19 patients (n = 125)	Methylprednisolone 250 mg/day for 3 days (n=63)  Versus  Dexamethasone 6 mg/day for up to 10 days (n=60)	Mortality, Need for ICU admission, Non-invasive Respiratory Support within 28 days, High-flow Oxygen Support within 28 days, Length of stay, Adverse events	Randomized Controlled Trial
Ranjbar 2021	Severe and critical COVID-19 patients (n = 86)	Methylprednisolone 2 mg/kg/day for 10 days (n=44)  Versus  Dexamethasone 6 mg/day for up to 10 days (n=42)	All-cause mortality in 28 days, Clinical status at 5 as well as 10 days after enrollment with 9-point WHO Ordinal Scale,	Randomized Controlled Trial
Saeed 2022	Severe and critical COVID-19 patients (n = 414)	Methylprednisolone 2 mg/kg/day for 10 days (n=222)  Versus  Dexamethasone 6 mg/day for up to 10 days (n=192)	All-cause mortality in 28 days, Length of stay, Duration of mechanical ventilation, Radiologic improvement using HRCT, Laboratory markers on admission and at Day 10: serum ferritin, d-dimer, CRP, LDH, N:L ratio	Randomized Controlled Trial
Soliman 2021	Severe and critical COVID-19 patients (n = 60)	Methylprednisolone 2 mg/kg/day for 10 days (n=30)  Versus  Dexamethasone 6 mg/day for up to 10 days (n=30)	Mortality rate, Need for ventilation, Need for ventilation and/or oxygenation, Inflammatory markers on admission and at day 5: N:L ration, interleukin 6, C-reactive protein	Randomized Controlled Trial



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**Table 3C. Characteristics of Included Studies for Standard-dose versus High-dose dexamethasone**

Study ID	Patients (n)	Interventions	Outcomes	Method
COVID STEROID 2 2021	Severe and critical COVID-19 patients (n = 968)	Dexamethasone (6 mg/day versus 12 mg/day) and standard of care	All-cause Mortality, Life Support-free Days, Ventilator-free Days, Cardiovascular Support-free Days, Renal Replacement Therapy-free Days, Adverse Events	Randomized Controlled Trial
COVIDICUS Trial 2022	Severe and critical COVID-19 patients (n = 546)	Dexamethasone (6 mg/day versus 20 mg/day) and standard of care	Time to all-cause mortality at day 60 and time to IMV requirements assessed at day 28	Randomized Controlled Trial
Maskin 2022	Severe and critical COVID-19 patients (n = 98)	Dexamethasone (6 mg/day versus 16 mg/day) and standard of care	Ventilator-free days at 28 days, all-cause mortality, infection rate, muscle weakness, and glycemic control	Randomized Controlled Trial
Taboada 2021	Severe and critical COVID-19 patients (n = 200)	Dexamethasone (6 mg/day versus 20 mg/day) and standard of care	Clinical worsening within 11 days, Time to recovery, admission to ICU, length of ICU stay, mechanical ventilation requirement, duration of mechanical ventilation, in-hospital mortality, nosocomial infection, insulin use for hyperglycemia, thrombosis	Randomized Controlled Trial



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Toroghi 2021	Severe and critical COVID-19 patients (n = 133)	Dexamethasone (6 mg/day versus 24 mg/day) and standard of care	Need for mechanical ventilation, duration of mechanical ventilation, duration of hospital stay, need for ICU admission, duration of ICU stay, mortality at 60 days	Randomized Controlled Trial
Wu 2022	Severe and critical COVID-19 patients (n = 107)	Dexamethasone (6 mg/day versus 20 mg/day) and standard of care	WHO-OSCI for clinical improvement at days 14 and 28, ICU-free days in first 28 days, ventilator-free days in first 28 days, SOFA score at randomization and at 48 hours	Randomized Controlled Trial





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**Table 3D. Characteristics of Included Studies for Timing of Corticosteroids**

Study ID	Patients (n)	Interventions	Comparator	Outcomes
Bahl 2021	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 2021	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



## Philippine COVID-19 Living Clinical Practice Guidelines

**Table 3D. Characteristics of Included Studies for Timing of Corticosteroids (continued)**

Study ID	Patients (n)	Interventions	Comparator	Outcomes
Monedero 2021]	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 2021	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



## Philippine COVID-19 Living Clinical Practice Guidelines

**Table 3D. Characteristics of Included Studies for Timing of Corticosteroids (continued)**

Study ID	Patients (n)	Interventions	Comparator	Outcomes
Dupuis 2021	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
Moreno 2021	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



## Philippine COVID-19 Living Clinical Practice Guidelines

Table 3D. Characteristics of Included Studies for Timing of Corticosteroids (continued)

Study ID	Patients (n)	Interventions	Comparator	Outcomes
Li 2020	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



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Lamouche-Wilquin 2022	Critical COVID-19 (n=670)	Timing: within 24 hours of ICU admission  Dexamethasone 6 mg/day intravenously or Prednisolone equivalent  Plus Standard of Care	Timing: within 24 hours of ICU admission  Methylprednisolone or Prednisolone equivalent  Plus Standard of Care	Ventilator-associated pneumonia  Mortality  SOFA Score
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## Philippine COVID-19 Living Clinical Practice Guidelines

**Table 3E. Characteristics of Included Studies for Corticosteroids in Pediatric Severe to Critical COVID-19**

<b>Study ID</b>	<b>Patients (n)</b>	<b>Interventions</b>	<b>Comparator</b>	<b>Outcomes</b>
Gonzalez-Dambrauskas 2022	Pediatric critical COVID-19 (n=557)  Subgroup: Pediatric critical COVID-19 without Multisystem Inflammatory Syndrome in Children (MIS-C) (n=367)	Corticosteroids:  Dexamethasone (dose and duration not specified)  Methylprednisolone (dose and duration not specified)  Plus, Standard of Care	No corticosteroids  Plus, Standard of Care	Mortality



# Philippine COVID-19 Living Clinical Practice Guidelines

## Appendix 5: Risk of Bias Assessment

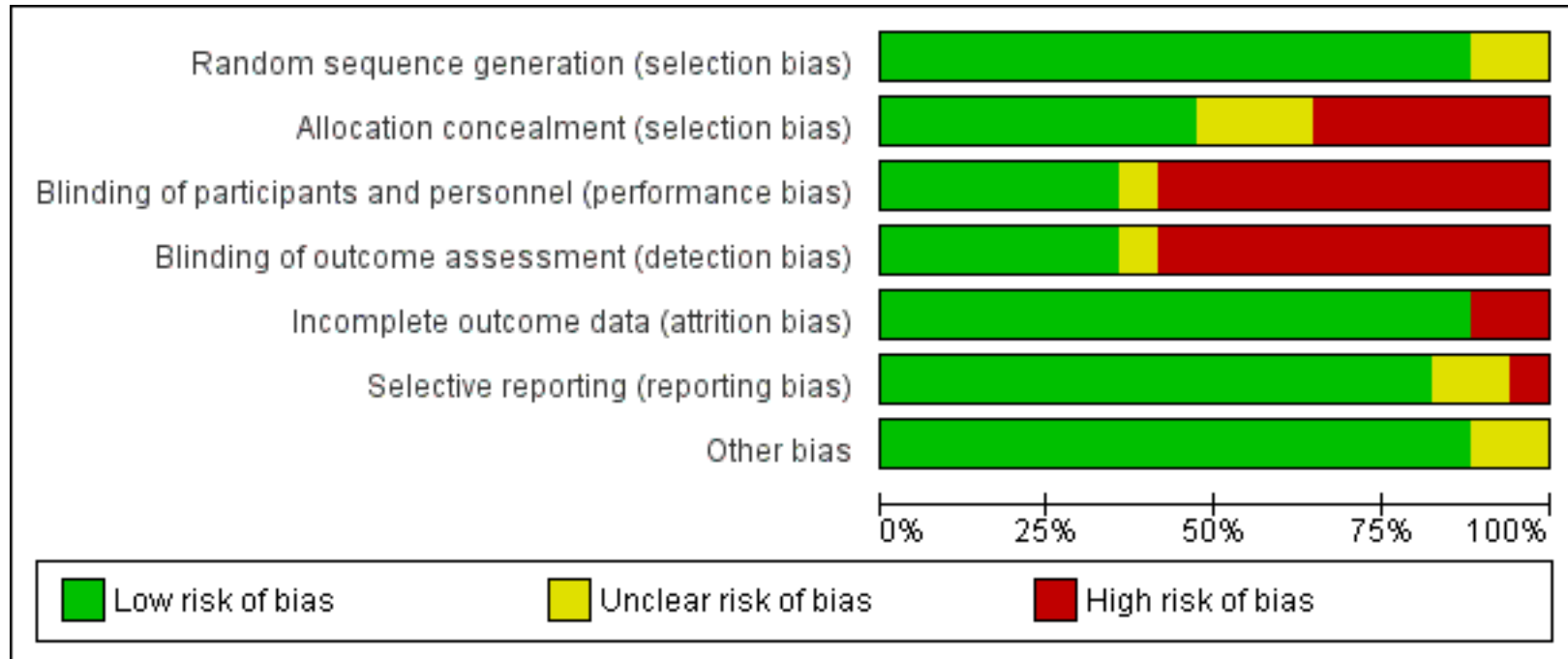


Figure 2A. Risk of Bias Graph for Type and Dosing of Corticosteroids



## Philippine COVID-19 Living Clinical Practice Guidelines

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CAPE COVID 2020	+	+	+	+	+	+	+
CoDEX 2020	+	-	-	-	+	+	+
COVID STEROID 2021	+	+	+	+	+	+	+
COVID STEROID 2 2021	+	+	+	+	+	+	+
DEXA-COVID 19 2020	?	?	-	-	-	?	?
Edalatfard 2020	+	+	-	-	+	+	+
Farahani 2020	+	+	+	+	+	-	+
Ghanel 2021	+	-	-	-	+	+	+
GLUCCOVID 2021	+	-	-	-	+	+	+
Jamaati 2021	+	?	?	?	+	+	+
Jeronimo 2021	+	+	+	+	+	+	+
Ranjbar 2021	+	+	+	+	+	+	+
RECOVERY 2021	+	-	-	-	+	+	+
REMAP-CAP 2020	+	-	-	-	+	+	+
Solanich 2021	+	-	-	-	+	+	+
Steroids-SARI 2020	?	?	-	-	-	?	?
Tang 2021	+	+	-	-	+	+	+

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





## Philippine COVID-19 Living Clinical Practice Guidelines

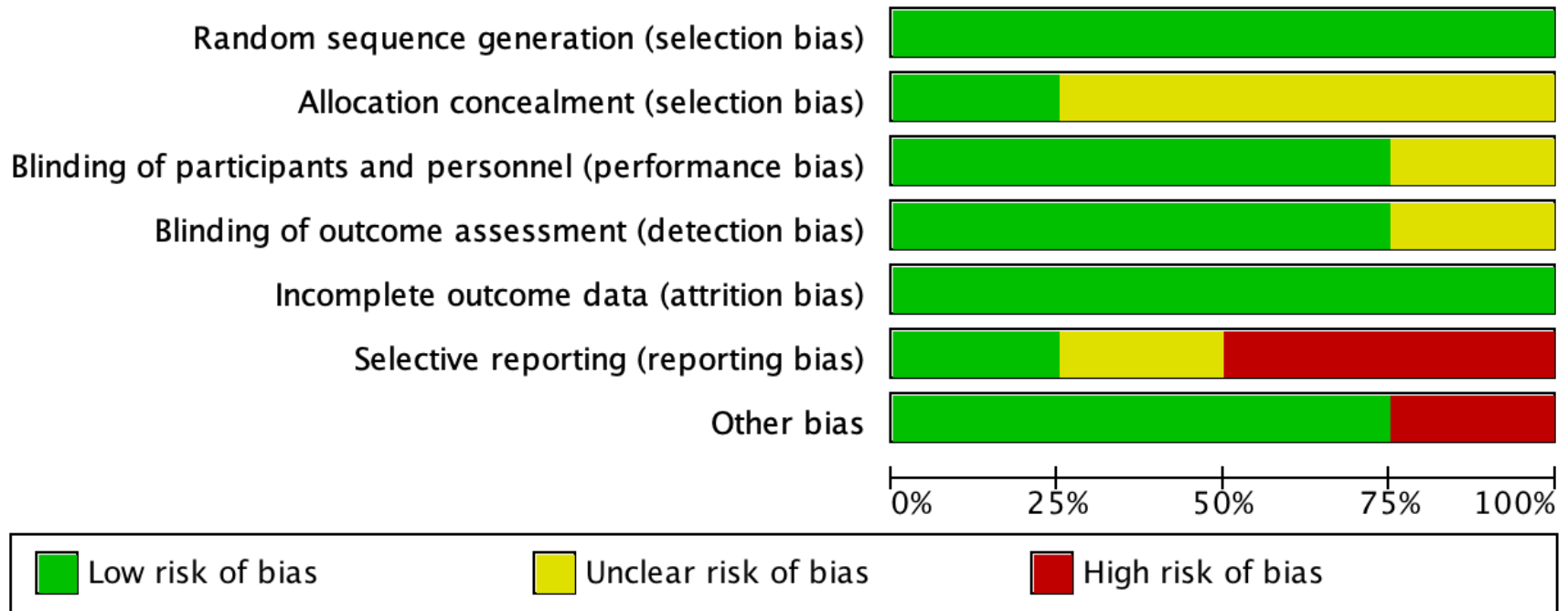


Figure 3A. Risk of Bias Graph for Methylprednisolone versus Dexamethasone



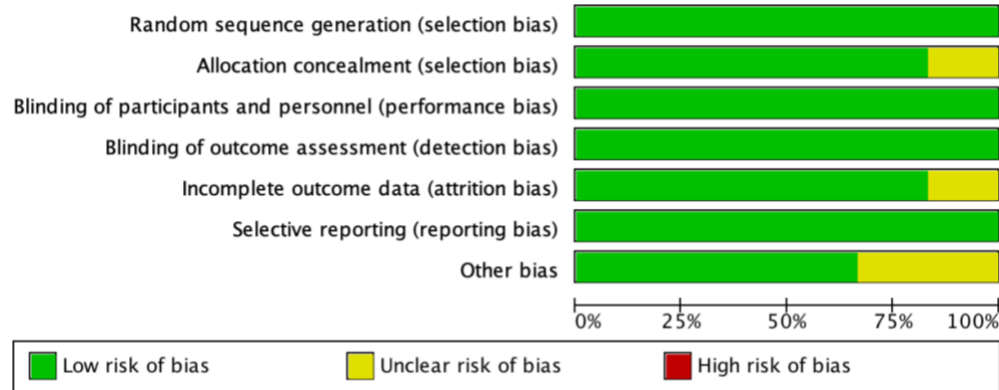
## Philippine COVID-19 Living Clinical Practice Guidelines

	Solimman 2022	Saeed 2022	Ranjbar 2021	Corral-Gudino 2022	
	+	+	+	+	Random sequence generation (selection bias)
	+	?	?	?	Allocation concealment (selection bias)
	+	+	+	?	Blinding of participants and personnel (performance bias)
	+	+	+	?	Blinding of outcome assessment (detection bias)
	+	+	+	+	Incomplete outcome data (attrition bias)
	?	-	-	+	Selective reporting (reporting bias)
	+	-	+	+	Other bias

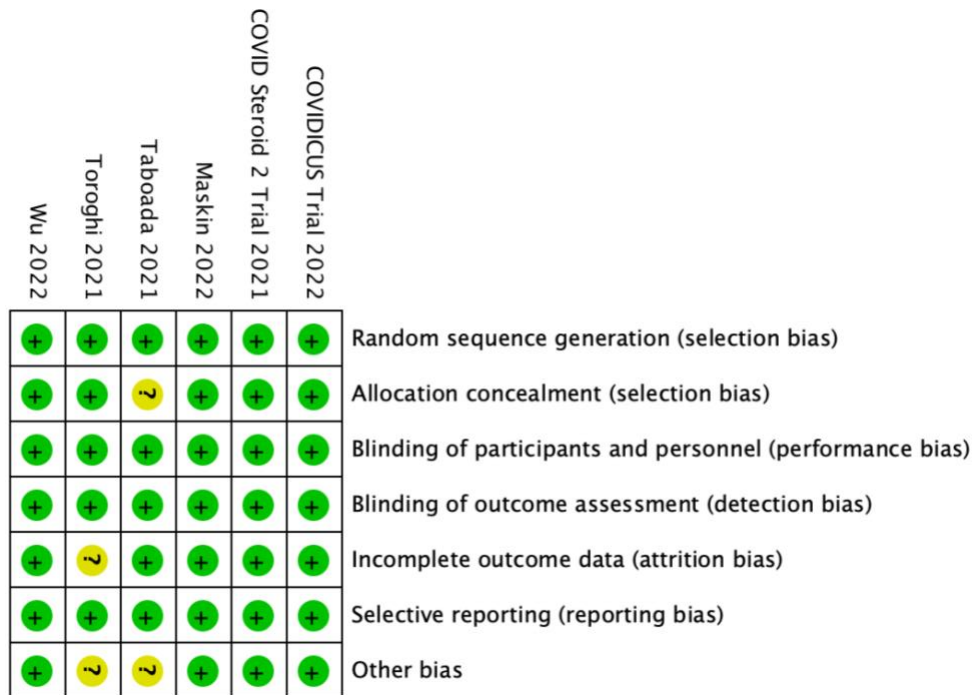
Figure 3B. Risk of Bias Summary for Methylprednisolone versus Dexamethasone



# Philippine COVID-19 Living Clinical Practice Guidelines



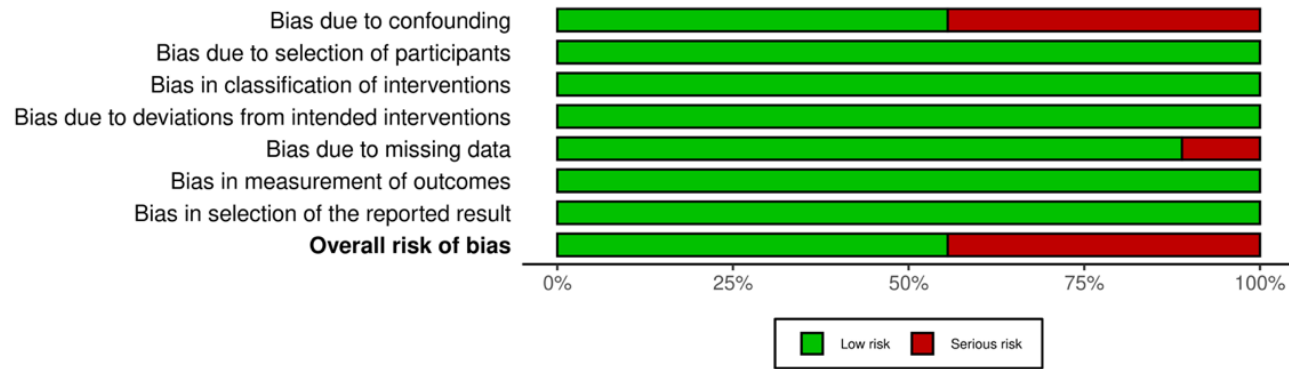
**Figure 4A.** Risk of Bias Graph for Standard versus High-dose Dexamethasone



**Figure 4B.** Risk of Bias Summary for Standard versus High-dose Dexamethasone



# Philippine COVID-19 Living Clinical Practice Guidelines



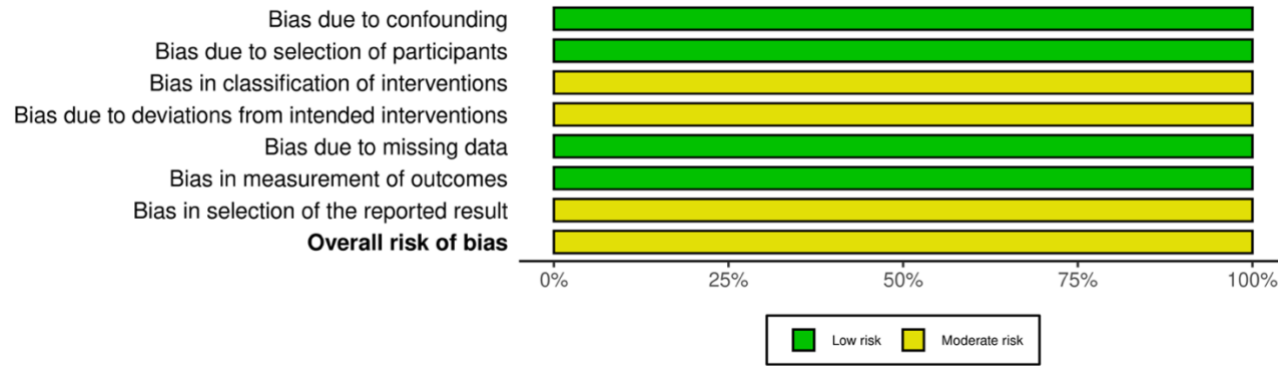
**Figure 5A.** Risk of Bias Graph for Timing of Corticosteroids



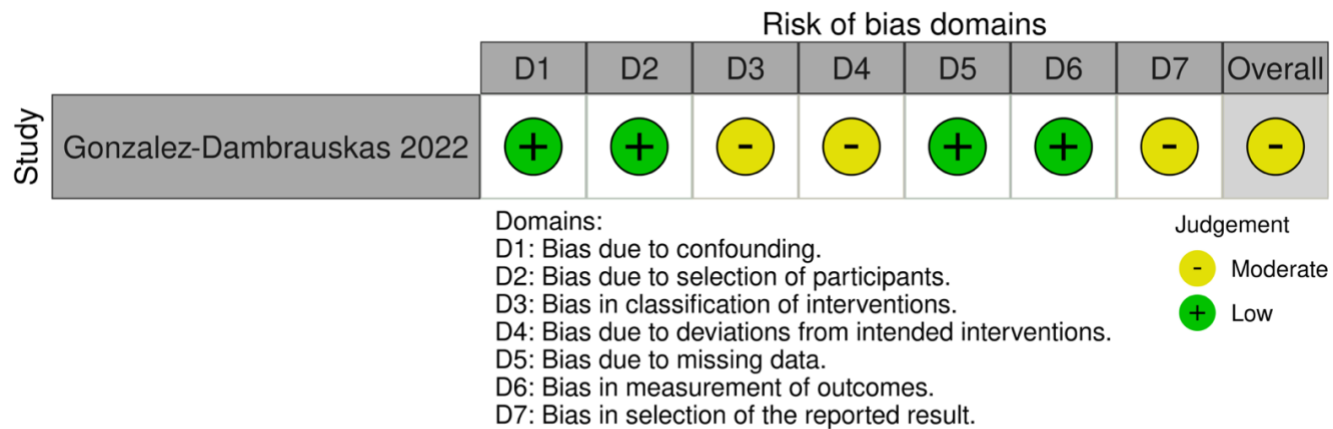
**Figure 5B.** Risk of Bias Summary for Timing of Corticosteroids Using ROBINS-I



# Philippine COVID-19 Living Clinical Practice Guidelines



**Figure 6A.** Risk of Bias Graph for Corticosteroids in the Pediatric Population



**Figure 6B.** Risk of Bias Summary for Corticosteroids in the Pediatric Population



# Philippine COVID-19 Living Clinical Practice Guidelines

## Appendix 6.1: 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 4. Summary of Findings Table (IV Corticosteroids vs. Standard Care or Placebo)**

Certainty Assessment							No of Patients		Effect		Certainty
No of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	IV Corticosteroids	Control	Relative (95% CI)	Absolute (95% CI)	
<b>All-cause Mortality (All Corticosteroids)</b>											
14	randomized trials	not serious	not serious	serious <sup>c</sup>	not serious	none	703/2629 (26.7%)	1269/4230 (30.0%)	RR 0.87 (0.78-0.97)	39 fewer per 1,000 (from 66 fewer to 9 fewer)	⊕⊕⊕○ MODERATE
<b>All-cause Mortality (Dexamethasone Group)</b>											
4	randomized trials	not serious	not serious	serious <sup>c</sup>	not serious	none	497/1786 (27.8%)	1079/3472 (31.1%)	RR 0.86 (0.79-0.94)	44 fewer per 1,000 (from 65 fewer to 19 fewer)	⊕⊕⊕○ MODERATE
<b>All-cause Mortality (Hydrocortisone Group)</b>											
3	randomized trials	not serious	not serious	not serious	serious <sup>d,e</sup>	none	96/369 (26.0%)	56/188 (29.8%)	RR 0.85 (0.50-1.44)	45 fewer per 1,000 (from 149 fewer to 131 more)	⊕⊕⊕○ MODERATE
<b>All-cause Mortality (Methylprednisolone Group)</b>											
4	randomized trials	not serious	not serious	not serious	serious <sup>d</sup>	none	106/357 (29.7%)	122/350 (34.9%)	RR 0.82 (0.59-1.16)	63 fewer per 1,000 (from 143 fewer to 56 more)	⊕⊕⊕○ MODERATE
<b>All-cause Mortality (Prednisolone Group)</b>											
1	randomized trials	not serious	not serious	not serious	serious <sup>d</sup>	none	4/116 (3.4%)	12/220 (5.5%)	RR 0.63 (0.21-1.92)	20 fewer per 1,000 (from 43 fewer to 50 more)	⊕⊕⊕○ MODERATE
<b>COVID-19-related Mortality</b>											
1	randomized trials	not serious	not serious	not serious	serious <sup>d,f,g</sup>	none	4/27 (14.8%)	4/28 (14.3%)	RR 1.04 (0.29-3.73)	6 more per 1,000 (from 101 fewer to 390 more)	⊕⊕⊕○ MODERATE



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Certainty Assessment							No of Patients		Effect		Certainty
No of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	IV Corticosteroids	Control	Relative (95% CI)	Absolute (95% CI)	
<b>Time to Death (All-cause)</b>											
1	randomized trials	not serious	not serious	not serious	serious <sup>d</sup>	none	27 participants	28 participants	HR 0.80 (0.24-2.61)	--	⊕⊕⊕○ MODERATE
<b>Time to Death (COVID-19-related)</b>											
1	randomized trials	not serious	not serious	not serious	serious <sup>d</sup>	none	27 participants	28 participants	HR 0.96 (0.24-3.84)	--	⊕⊕⊕○ MODERATE
<b>Time to Clinical Improvement</b>											
2	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>d</sup>	none	70 participants	71 participants	HR 0.93 (0.65-1.33)	--	⊕⊕○○ LOW
<b>Length of Hospital Stay (Dexamethasone)</b>											
1	randomized trials	not serious	not serious	not serious	serious <sup>f</sup>	none	25	35	--	MD 4.80 day higher (3.06 higher to 6.54 higher)	⊕⊕⊕○ MODERATE
<b>Length of Hospital Stay (Methylprednisolone and Prednisolone)</b>											
3	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>d,e</sup>	none	337	406	--	MD 0.28 day lower (1.62 lower to 1.07higher)	⊕⊕○○ LOW
<b>ICU Admission</b>											
2	randomized trials	serious <sup>a</sup>	not serious	not serious	serious <sup>d</sup>	none	7/159 (4.4%)	15/263 (5.7%)	RR 0.78 (0.32-1.90)	13 fewer per 1,000 (from 39 fewer to 51 more)	⊕⊕○○ LOW
<b>Length of ICU Stay</b>											
1	randomized trials	not serious	not serious	not serious	not serious	none	25	25	--	MD 4.2 days more (3.26 more to 5.14 more)	⊕⊕⊕⊕ HIGH



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





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

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



# Philippine COVID-19 Living Clinical Practice Guidelines

**Table 5. Summary of Findings Table Methylprednisolone versus Dexamethasone**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	methylprednisolone	dexamethasone	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality All-cause (follow-up: mean 28 days)</b>												
4	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	61/359 (17.0%)	172/327 (52.6%)	<b>RR 0.37</b> (0.24-0.58)	<b>331 fewer per 1,000</b> (from 400 fewer to 221 fewer)	⊕⊕⊕○ Moderate	CRITICAL
<b>Need for Mechanical Ventilation</b>												
3	randomised trials	serious <sup>b</sup>	serious <sup>c</sup>	not serious	serious <sup>d</sup>	none	26/135 (19.3%)	28/134 (20.9%)	<b>RR 1.04</b> (0.41-2.65)	<b>8 more per 1,000</b> (from 123 fewer to 345 more)	⊕○○○ Very low	CRITICAL
<b>O2 Support Escalation</b>												
2	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	29/93 (31.2%)	36/92 (39.1%)	<b>RR 0.78</b> (0.59-1.03)	<b>86 fewer per 1,000</b> (from 160 fewer to 12 more)	⊕⊕○○ Low	CRITICAL
<b>WHO Ordinal Scale for Clinical Improvement at Day 5</b>												
1	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>f</sup>	none	42	44	-	<b>MD 1.19 pts lower</b> (1.9 lower to 0.48 lower)	⊕⊕○○ Low	IMPORTANT
<b>WHO Ordinal Scale for Clinical Improvement at Day 7</b>												
1	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>g</sup>	none	42	44	-	<b>MD 1.81 pts lower</b> (2.8 lower to 0.79 lower)	⊕⊕○○ Low	IMPORTANT
<b>Adverse Events: Secondary Infection</b>												
1	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>d</sup>	none	7/63 (11.1%)	8/62 (12.9%)	<b>RR 0.86</b> (0.33-2.23)	<b>18 fewer per 1,000</b> (from 86 fewer to 159 more)	⊕○○○ Very low	CRITICAL

Adverse Events: Hyperglycemia



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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	methylprednisolone	dexamethasone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>a</sup>	none	17/63 (27.0%)	5/62 (8.1%)	<b>RR 3.35</b> (1.32-8.51)	<b>190 more per 1,000</b> (from 26 more to 606 more)	⊕⊕○○ Low	CRITICAL
<b>C-Reactive Protein</b>												
2	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	222	192	-	<b>MD 50.57 lower</b> (55.3 lower to 45.85 lower)	⊕⊕○○ Low	IMPORTANT
<b>N:L Ratio</b>												
2	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	222	192	-	<b>MD 6.97 lower</b> (12.09 lower to 1.84 lower)	⊕⊕○○ Low	IMPORTANT
<b>Interleukin-6</b>												
1	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	30	30	-	<b>MD 22.9 lower</b> (26.4 lower to 19.38 lower)	⊕⊕○○ Low	IMPORTANT
<b>Serum Ferritin</b>												
1	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	222	192	-	<b>MD 56.3 lower</b> (99.93 lower to 12.67 lower)	⊕⊕○○ Low	IMPORTANT
<b>D-dimer</b>												
1	randomised trials	serious <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	222	192	-	<b>MD 1.1 lower</b> (1.35 lower to 0.85 lower)	⊕⊕○○ Low	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio



# Philippine COVID-19 Living Clinical Practice Guidelines

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## *Explanations*

- a. One study (Saeed 2022) used censored analysis and Two studies (Ranjbar 2021 and Saeed 2021) had unclear bias on allocation concealment
- b. One study (Ranjbar 2021) has unclear risk of bias due to allocation concealment
- c. Significant heterogeneity
- d. Wide confidence interval
- e. The study (Corral-Gudino 2022) Unclear risk of bias in allocation concealment and blinding
- f. Small sample size / optimal information size from a single study and imprecision
- g. Small sample size / optimal information size from a single study
- h. One study (Saeed 2022) used censored analysis
- i. Small sample size / optimal information size from two studies



# Philippine COVID-19 Living Clinical Practice Guidelines

**Table 6. Summary of Findings Table Standard-dose versus High-dose Dexamethasone**

Certainty assessment							No of patients		Effect		Certainty	Importance	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high-dose	standard-dose dexamethasone	Relative (95% CI)	Absolute (95% CI)			
<b>All-cause mortality at 28 days</b>													
5	randomised trials	not serious	not serious	not serious	serious*	none	We performed generic inverse variance analysis using pooled adjusted (COVID Steroid 2 Trial 2021; Taboada 2021) and unadjusted (COVIDICUS Trial 2022; Maskin 2022; Wu 2022) risk ratio (RR 0.97, 95% 0.81-1.15, I <sup>2</sup> =30%)		⊕⊕⊕○	Moderate	CRITICAL		
<b>All-cause mortality at 60 days</b>													
3	randomised trials	not serious	not serious	not serious	serious*	none	We performed generic inverse variance analysis using pooled adjusted (Taboada 2021) and unadjusted (COVIDICUS Trial 2022; Toroghi 2021) risk ratio (RR 1.20, 95% 0.69-2.10, I <sup>2</sup> =0%)		⊕⊕⊕○	Moderate	CRITICAL		
<b>All-cause mortality at 90 days</b>													
2	randomised trials	not serious	not serious	not serious	serious*	none	We performed generic inverse variance analysis using pooled adjusted (COVID Steroid 2 Trial 2021) and unadjusted (Maskin 2022) risk ratio (RR 0.90, 95% 0.74-1.09, I <sup>2</sup> =5%)		⊕⊕⊕○	Moderate	CRITICAL		
<b>Need for mechanical ventilation</b>													
2	randomised trials	not serious	not serious	not serious	serious*	none	21/184 (11.4%)	12/149 (8.1%)	RR 1.39 (0.69-2.80)	31 more per 1,000 (from 25 fewer to 145 more)	⊕⊕⊕○	Moderate	CRITICAL
<b>Adverse Events: Infection-relate</b>													
5	randomised trials	not serious	not serious	not serious	serious*	none	We performed generic inverse variance analysis using pooled adjusted (COVID Steroid 2 Trial 2021; Taboada 2021) and unadjusted (COVIDICUS Trial 2022; Toroghi 2021; Wu 2022) risk ratio (RR 0.89, 95% 0.63-1.24, I <sup>2</sup> =0%)		⊕⊕⊕○	Moderate	CRITICAL		
<b>Adverse Events: Hyperglycemia and Insulin Therapy</b>													
3	randomised trials	not serious	not serious	not serious	serious*	none	We performed generic inverse variance analysis using pooled adjusted (Taboada 2021) and unadjusted (Toroghi 2021; Wu 2022) risk ratio (RR 1.10, 95% 0.86-1.41, I <sup>2</sup> =0%)		⊕⊕⊕○	Moderate	CRITICAL		
<b>Adverse Events: Thrombosis</b>													
2	randomised trials	not serious	not serious	not serious	serious*	none	We performed generic inverse variance analysis using pooled adjusted (Taboada 2021) and unadjusted (Toroghi 2021) risk ratio (RR 0.39, 95% 0.05-3.22, I <sup>2</sup> =26%)		⊕⊕⊕○	Moderate	CRITICAL		

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

**Explanations**



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- a. Confidence interval crossed the threshold

**Table 6. Summary of Findings Table Standard-dose versus High-dose Dexamethasone (continued)**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high-dose	standard-dose dexamethasone	Relative (95% CI)	Absolute (95% CI)		
<b>Ventilator-free days at 28 days</b>												
2	randomised trials	not serious	not serious	not serious	serious*	none	761	756	-	MD 0.11 days higher (0.47 lower to 0.69 higher)	⊕⊕⊕○ Moderate	IMPORTANT

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

**Explanations**

- a. Confidence interval crossed the threshold



# Philippine COVID-19 Living Clinical Practice Guidelines

## Appendix 6.2.: 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)**

No of Studies	Study Design	Certainty Assessment					No of Patients		Effect		Certainty	Importance
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Early Corticosteroids	Non-Early Corticosteroids	Relative (95% CI)	Absolute (95% CI)		
<b>Mortality (Intervention Cutoff: 24 Hours)</b>												
3	observational studies	not serious	not serious	not serious	not serious	none	183/676 (27.1%)	265/811 (32.7%)	OR 0.82 (0.53 - 1.25)	42 fewer per 1,000 (from 122 fewer to 51 fewer)	⊕⊕○○ LOW	CRITICAL
<b>Mortality (Intervention Cutoff: 48 Hours)</b>												
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 - 1.24)	5 fewer per 1,000 (from 59 fewer to 53 fewer)	⊕⊕○○ LOW	CRITICAL
<b>Mortality (Intervention Cutoff: 72 Hours)</b>												
3	observational studies	serious <sup>a</sup>	not serious	not serious	not serious	none	380/758 (50.1%)	397/819 (48.5%)	OR 1.01 (0.81 - 1.25)	2 more per 1,000 (from 52 fewer to 56 more)	⊕⊕○○ LOW	CRITICAL
<b>Mortality (Intervention Cutoff: 120 Hours)</b>												
1	observational studies	not serious	not serious	not serious	serious <sup>b</sup>	none	67/233 (28.8%)	79/287 (27.5%)	OR 1.06 (0.72 - 1.56)	12 more per 1,000 (from 61 fewer to 97 more)	⊕○○○ VERY LOW	CRITICAL
<b>Need for Mechanical Ventilation</b>												
2	observational studies	not serious	not serious	not serious	not serious	none	5/47 (10.6%)	7/21 (33.3%)	OR 0.24 (0.07 - 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



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No of Studies	Study Design	Certainty Assessment					No of Patients		Effect		Certainty	Importance
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Early Corticosteroids	Non-Early Corticosteroids	Relative (95% CI)	Absolute (95% CI)		
<b>Adverse Events: Hyperglycemia</b>												
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 - 12.67)	448 more per 1,000 (from 308 more to 599 more)	⊕⊕○○ LOW	CRITICAL
<b>Adverse Events: Blood Stream Infection</b>												
1	observational studies	not serious	not serious	not serious	serious <sup>b</sup>	none	13/66 (19.7%)	30/237 (12.7%)	OR 1.69 (0.83 - 3.47)	70 more per 1,000 (from 19 fewer to 208 more)	⊕○○○ VERY LOW	CRITICAL
<b>Adverse Events: Incidence of Hospital-Acquired Pneumonia and Ventilator Acquired Pneumonia</b>												
2	observational studies	not serious	not serious	not serious	serious <sup>b</sup>	none	227/435 (52.2%)	217/538 (40.3%)	OR 1.27 (1.00 - 1.71)	59 more per 1,000 (from 0 fewer to 133 more)	⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; MD: mean difference

## Explanations

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





# Philippine COVID-19 Living Clinical Practice Guidelines

## Appendix 6.3. GRADE Evidence Profile for Corticosteroids in Children

**Question:** Should intravenous corticosteroids be used in COVID-19?  
**Patient or Population:** Severe and critical pediatric COVID-19 patients  
**Setting:** In-patients Setting  
**Intervention:** Corticosteroids  
**Comparison:** No Corticosteroids

**Table 8. GRADE Evidence Profile for Corticosteroids in Children**

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
<b>Mortality for Dexamethasone</b>									
1	observational studies	not serious	not serious	not serious	serious <sup>a</sup>	none	Multivariable association with mortality in the subset of children without multisystem inflammatory syndrome showed inconclusive effect on mortality (OR 0.97; 95% 0.49 to 1.91). Odds ratio was adjusted for sex, age less than 2 years, region, and Pediatric Risk of Mortality III (PRISM III).	⊕○○○ Very low	CRITICAL
<b>Mortality for Methylprednisolone</b>									
1	observational studies	not serious	not serious	not serious	serious <sup>a</sup>	none	Multivariable association with mortality in the subset of children without multisystem inflammatory syndrome showed inconclusive effect on mortality (OR 0.93; 95% 0.43 to 2.03). Odds ratio was adjusted for sex, age less than 2 years, region, and Pediatric Risk of Mortality III (PRISM III).	⊕○○○ Very low	CRITICAL

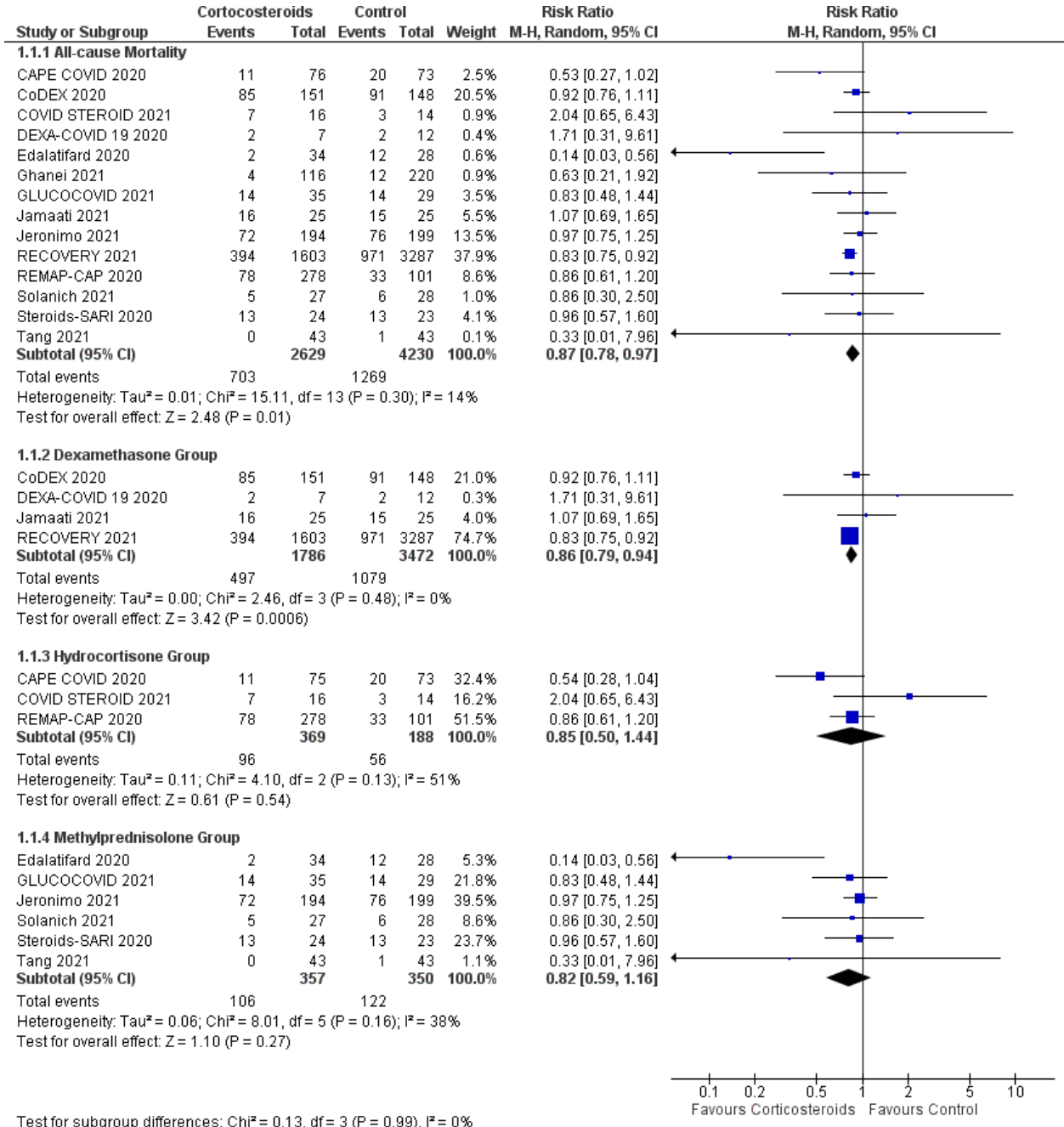
CI: confidence interval

### Explanations

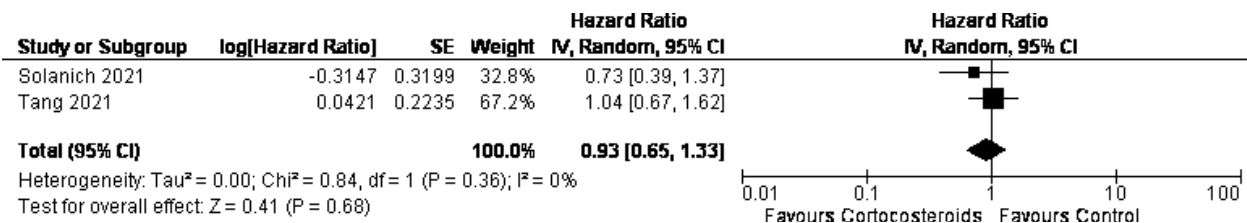
a. Wide confidence interval



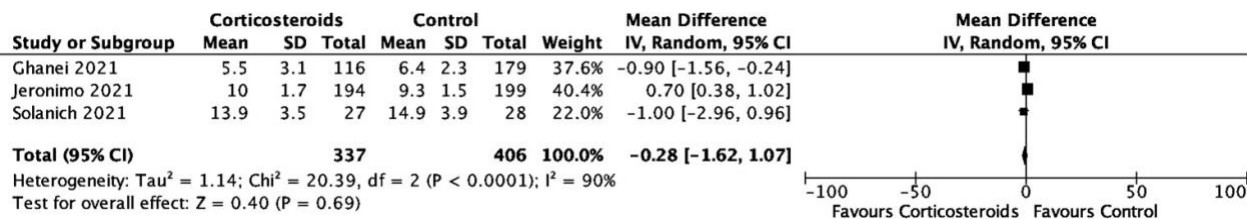
## Appendix 7: Forest Plots



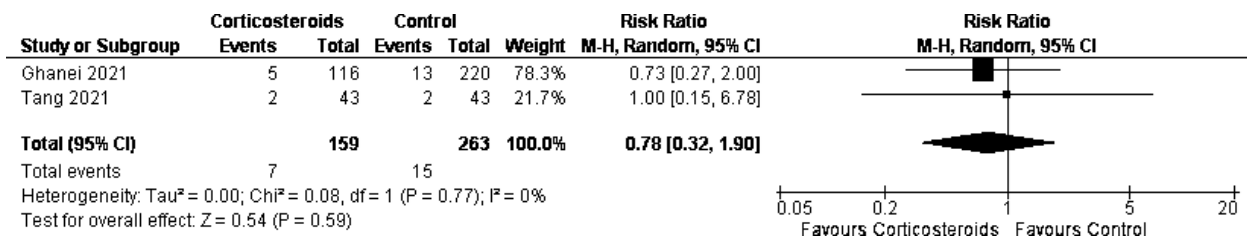
**Figure 7.** All-Cause Mortality Forest Plot for Type and Dosing of Corticosteroids



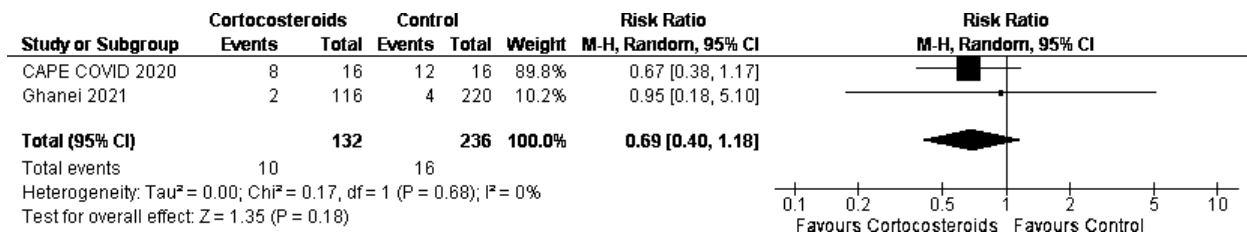
**Figure 8.** Time to Clinical Improvement Forest Plot for Type and Dosing of Corticosteroids



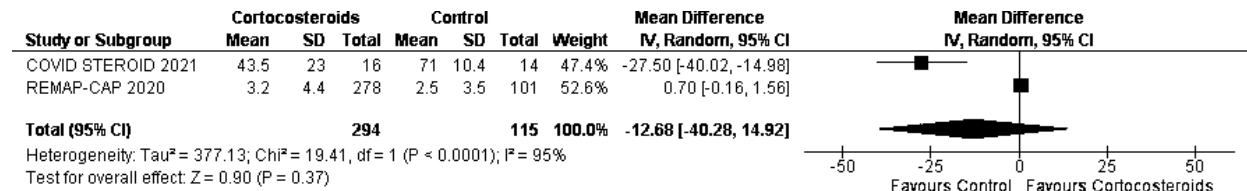
**Figure 9.** Length of Hospital Stay Forest Plot for Type and Dosing of Corticosteroids



**Figure 10.** ICU Admission Forest Plot for Type and Dosing of Corticosteroids



**Figure 11.** Intubation Rate Forest Plot for Type and Dosing of Corticosteroids



**Figure 12.** Life Support-free Days Forest Plot for Type and Dosing of Corticosteroid

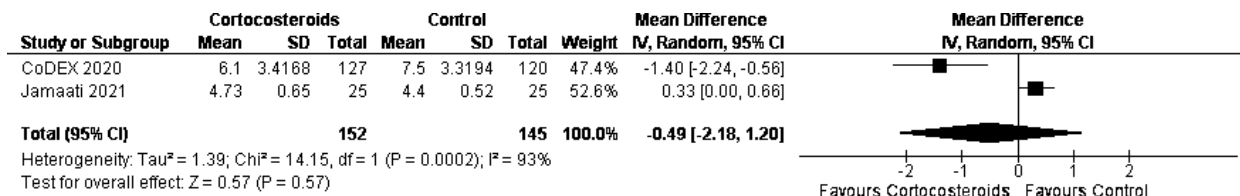


Figure 13. SOFA Score Forest Plot for Type and Dosing of Corticosteroids

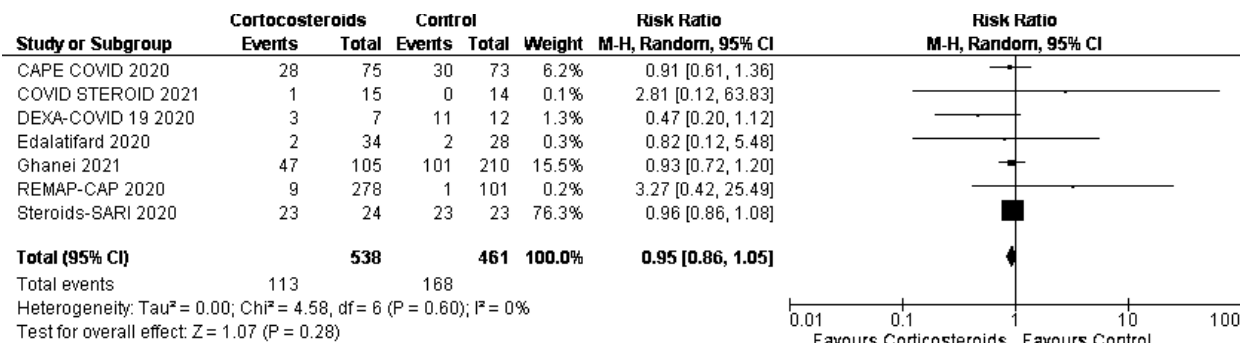


Figure 14. Adverse Events Forest Plot for Type and Dosing of Corticosteroids

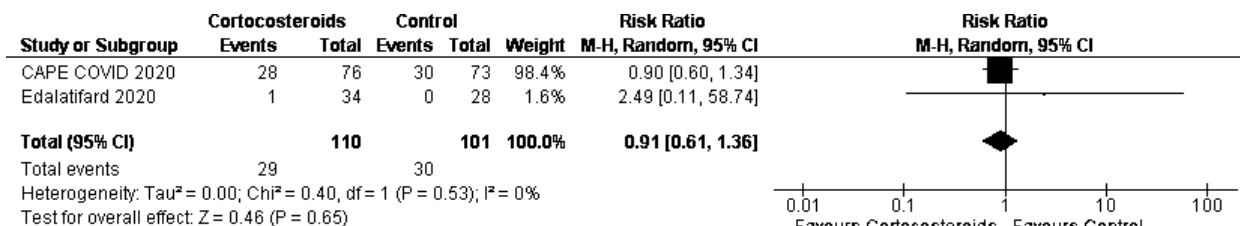


Figure 15. Nosocomial Infection Forest Plot for Type and Dosing of Corticosteroid

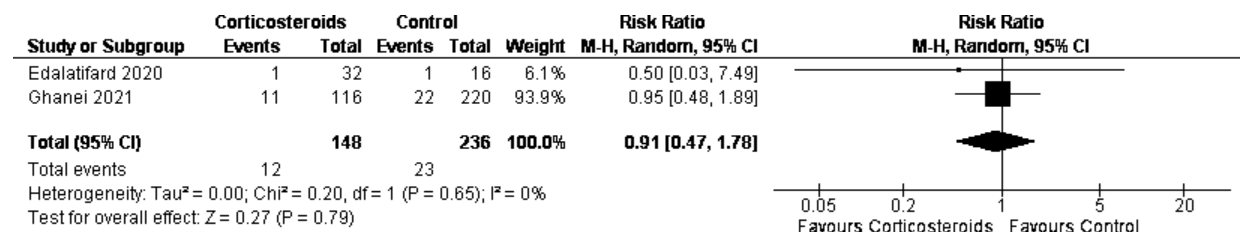


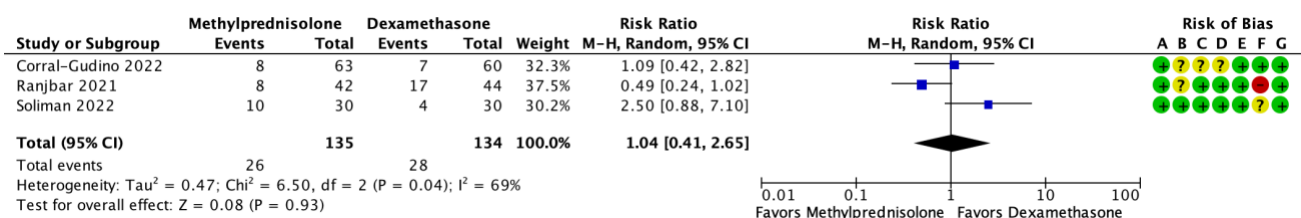
Figure 16. Gastrointestinal Symptoms Forest Plot for Type and Dosing of Corticosteroids



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

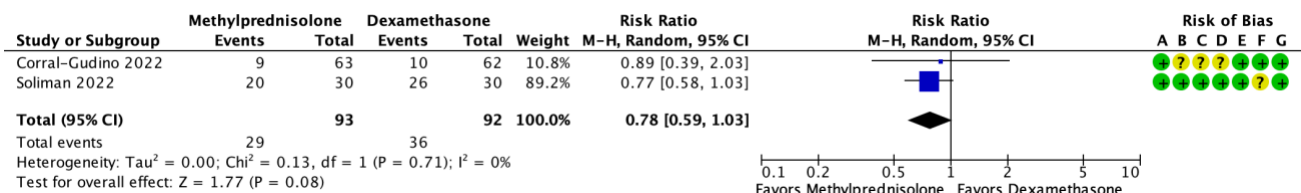
**Figure 17. Mortality for Methylprednisolone versus Dexamethasone**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 18. Need for Mechanical Ventilation for Methylprednisolone versus Dexamethasone**



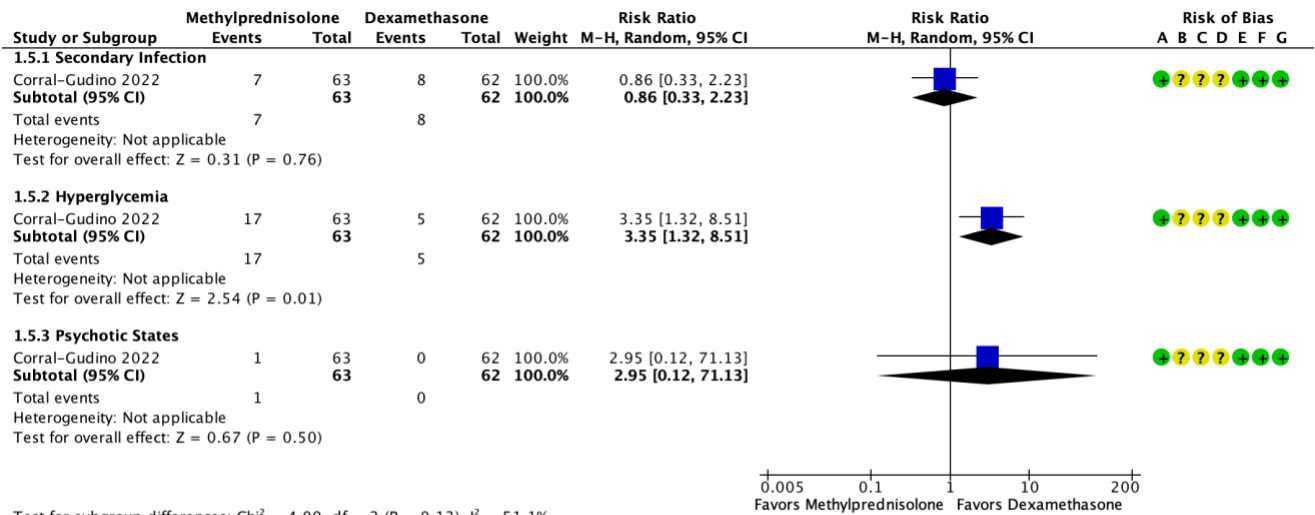
**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 19. Oxygen Support Escalation for Methylprednisolone versus Dexamethasone**



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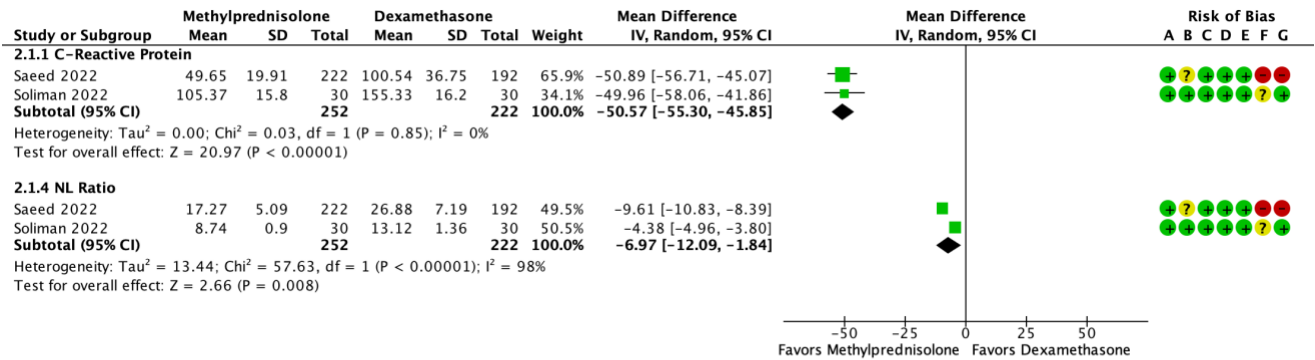


Test for subgroup differences: Chi<sup>2</sup> = 4.09, df = 2 (P = 0.13), I<sup>2</sup> = 51.1%

**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 20.** Forest Plot: Serious Adverse Events for Methylprednisolone versus Dexamethasone



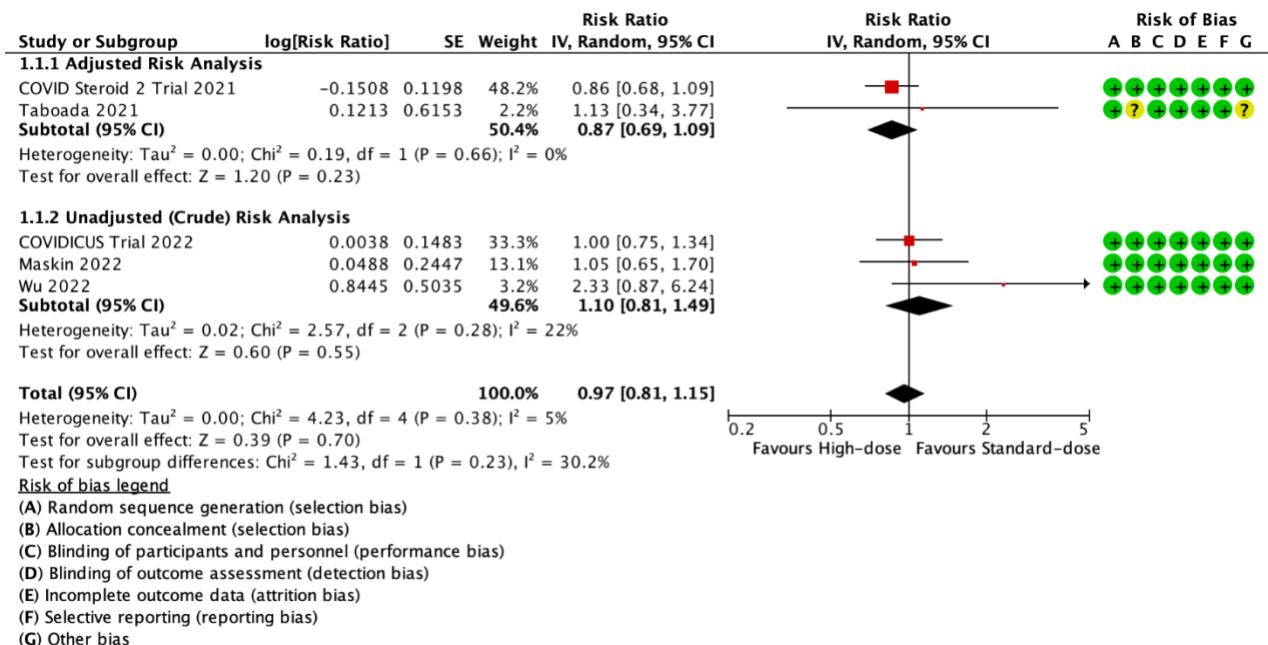
**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

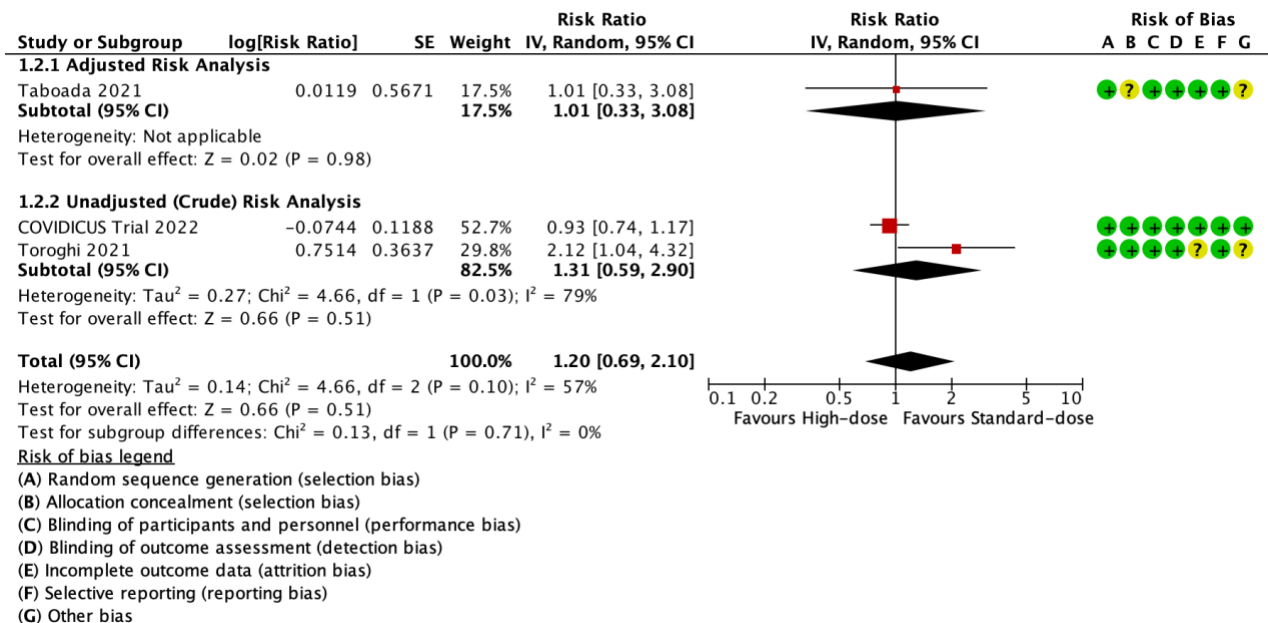
**Figure 21.** Forest Plot: Inflammatory Markers for Methylprednisolone versus Dexamethasone



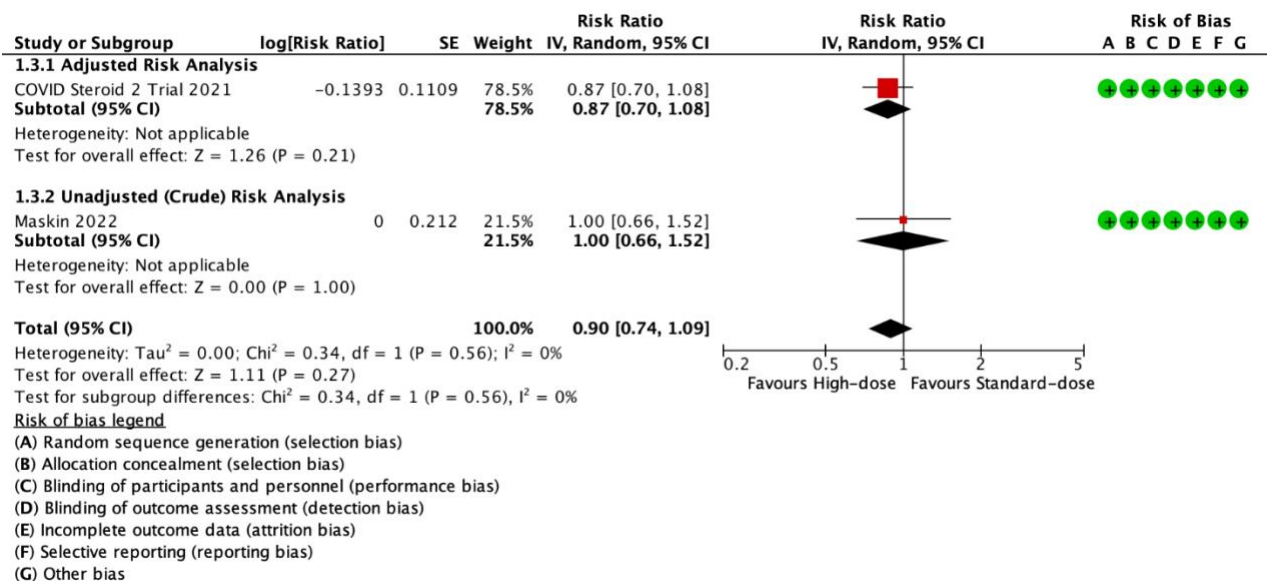
**Figure 22. Mortality Forest Plot for Standard-dose versus High-dose Dexamethasone**



**Figure 22A. All-cause mortality at 28 days after randomization**



**Figure 22B. All-cause mortality at 60 days after randomization**

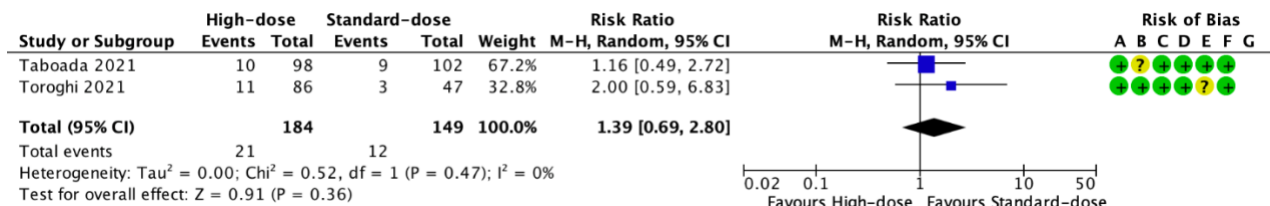


**Figure 22C.** All-cause mortality at 90 days after randomization





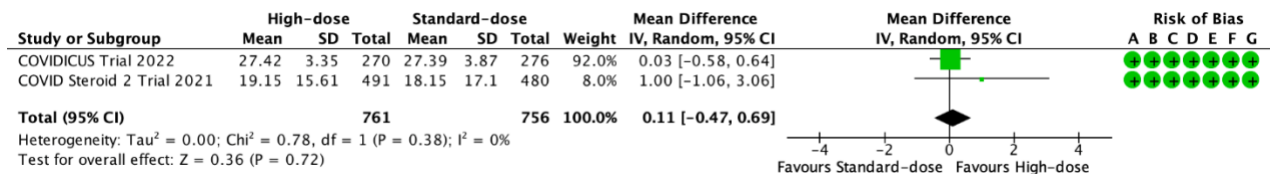
**Figure 23. Mechanical Ventilation Forest Plot for Standard-dose versus High-dose Dexamethasone**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 23A. Need for mechanical ventilation**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 23B. Ventilator-free days at 28 days after randomization**



Figure 24. Adverse Events Forest Plot for Standard-dose versus High-dose Dexamethasone

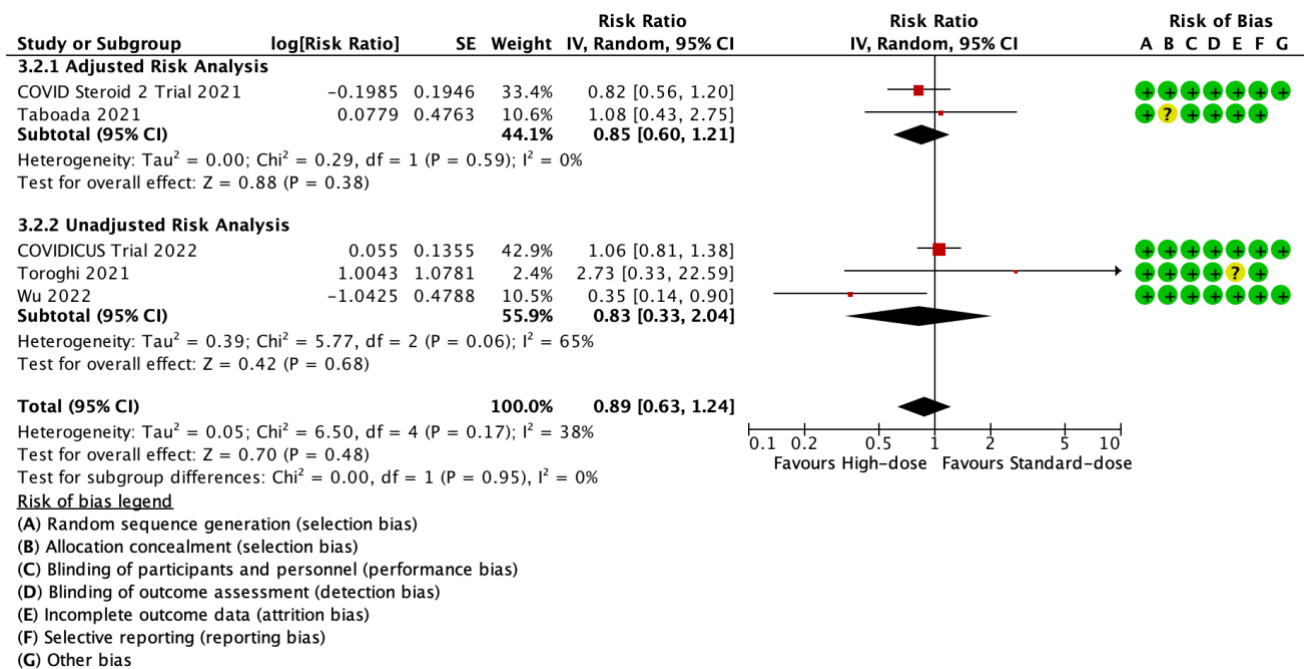


Figure 24A. Risk for Infection-related adverse events

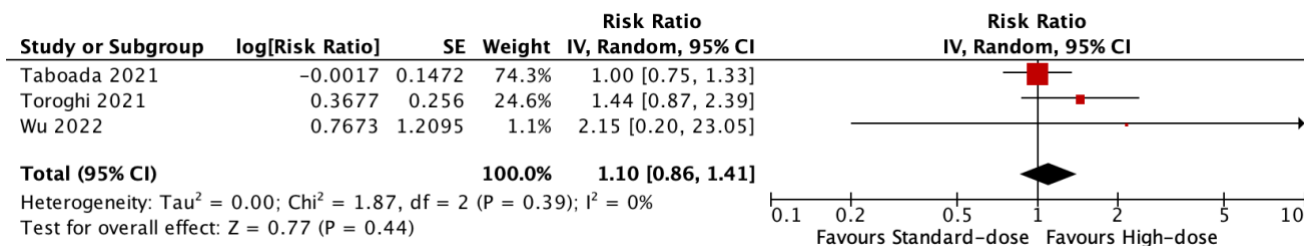


Figure 24B. Risk for Hyperglycemia

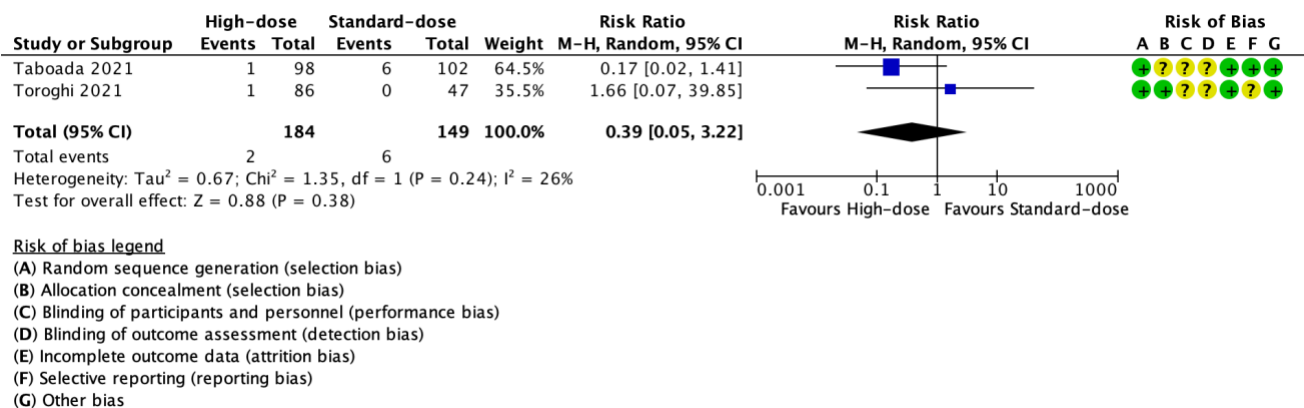
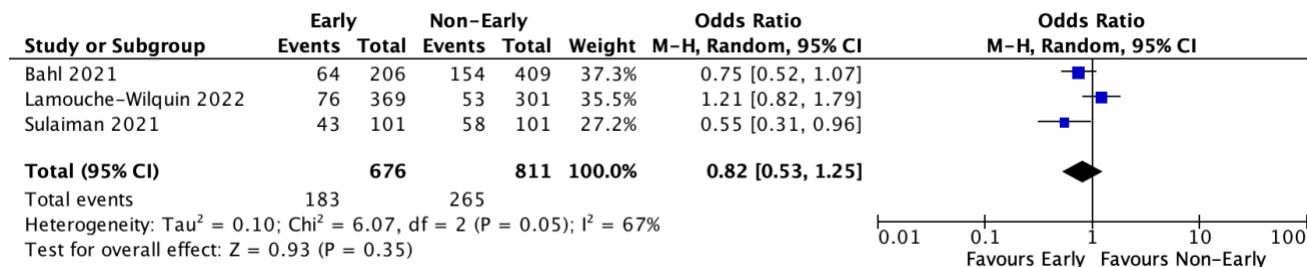


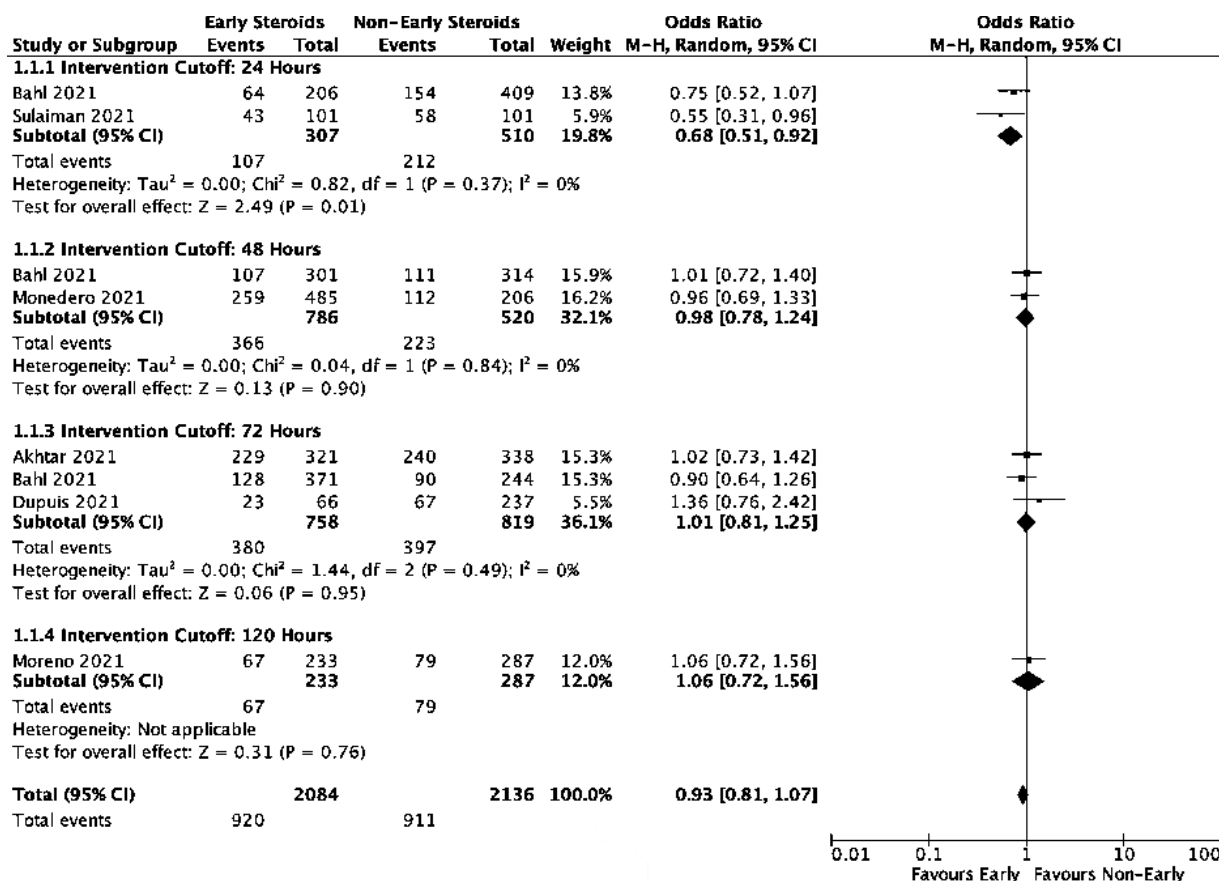
Figure 24C. Risk for thrombosis



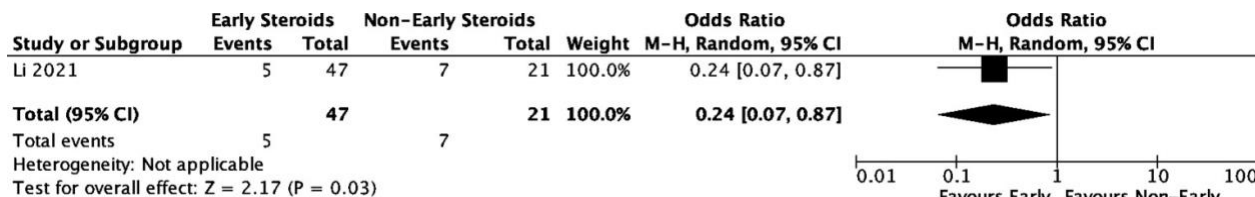
**Figure 25. Mortality Forest Plot for Early versus Non-Early Initiation of Corticosteroids**



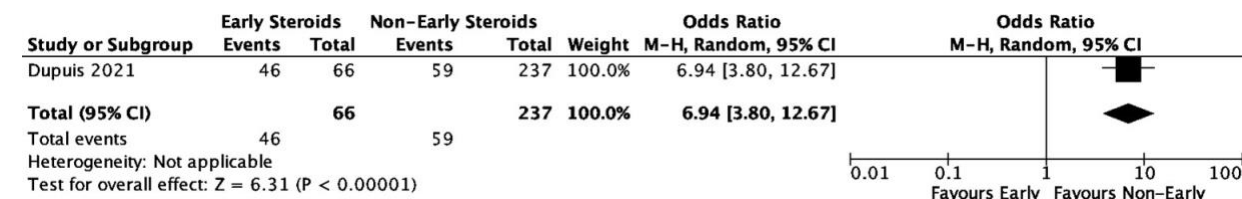
**Figure 25A. Updated Mortality Forest Plot for Early versus Non-Early Initiation of Corticosteroids for Intervention Cutoff: 24 Hours**



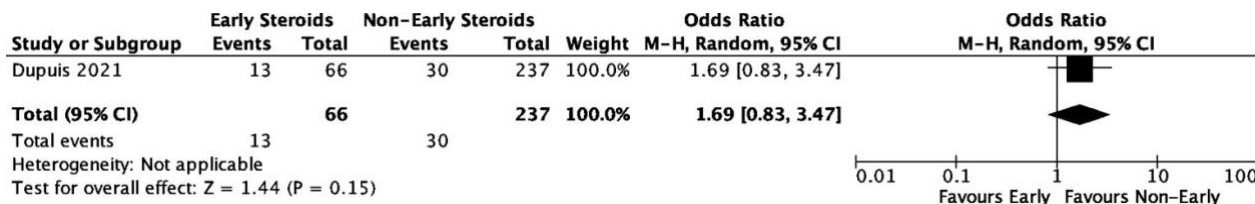
**Figure 25B. Mortality Forest Plot for Early versus Non-Early Initiation of Corticosteroids for Intervention Cutoff: 24 Hours**



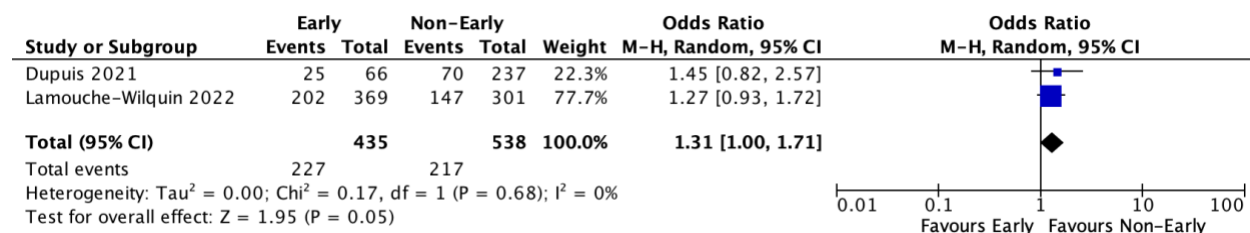
**Figure 26.** Need for Mechanical Ventilation Forest Plot for Early versus Non-Early Initiation of Corticosteroids



**Figure 27.** Adverse Events: Hyperglycemia Forest Plot for Early versus Non-Early Initiation of Corticosteroids



**Figure 28.** Adverse Events: Blood Stream Infection Forest Plot for Early versus Non-Early Initiation of Corticosteroids



**Figure 29.** Adverse Events: Incidence of Hospital-acquired Pneumonia and Ventilator-acquired Pneumonia Forest Plot for Early versus Non-Early Initiation of Corticosteroid



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### Appendix 8: Characteristics of Ongoing Studies

Title (NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
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
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
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
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



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Title (NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
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 (n=126)	June 10, 2021 – March 30, 2022  Spain  Recruiting as of 18 October 2022  Estimated Study Completion: March 2023
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	Adult patients 18 years old and above with mild to moderate COVID- 19 (n = 752)	February 10, 2021 – August 15, 2021  Cairo, Egypt  Completed as of 31 Jan 2022  Estimated Study Completion: 15 Dec 2021