Journal of Experimental Pharmacology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

The Efficacy of Oral/Intravenous Corticosteroid Use in COVID-19 Patients: A Systematic Review

Irma Rahayu Latarissa[1,2], Farida Rendrayani[1], Ghina Nadhifah Iftinan[2], Cecep Suhandi[3], Anna Meiliana[1,4], Ida Paulina Sormin[5,6], Melisa Intan Barliana[7,8], Keri Lestari[1,2,8]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia; [2]Medication Therapy Adherence Clinic (MTAC), Universitas Padjadjaran, Sumedang, Indonesia; [3]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia; [4]Prodia Clinical Laboratory, Central Jakarta, Indonesia; [5]Faculty of Pharmacy, University of 17 August 1945 Jakarta, Jakarta, Indonesia; [6]Prodia Diacro Laboratories, Jakarta, Indonesia; [7]Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia; [8]Center of Excellence for Pharmaceutical Care Innovation, Universitas Padjadjaran, Sumedang, Indonesia

Correspondence: Keri Lestari, Department of Pharmacology and Clinical PharmacyFaculty of Pharmacy, Universitas Padjadjaran, Jl. Raya Bandung Sumedang KM. 21, Jatinangor, 45363, Indonesia, Email lestarikd@unpad.ac.id

Abstract: The COVID-19 pandemic is prompting extensive investigation into potential treatments, including the use of corticosteroids to manage inflammation and mitigate severe disease outcomes. Therefore, this systematic review aimed to evaluate the efficacy of oral/intravenous corticosteroids in the management of COVID-19. A comprehensive search was conducted across major scientific databases such as MEDLINE, Scopus, and Cochrane for relevant studies published from 2019–2024. The inclusion criteria included studies investigating the use of oral/intravenous corticosteroids in COVID-19 patients >18 years with a randomized placebo-controlled trial method. Non-placebo-controlled studies, studies using combined treatments with other drugs, as well as protocol articles, conference proceedings, review articles, and non-English studies were excluded. A narrative synthesis approach was adopted given the significant methodological diversity. The results showed that a total of 12 studies met the inclusion criteria covering the use of three drugs, including dexamethasone (three), hydrocortisone (two), and methylprednisolone (seven). The outcome parameters used for each study were different. Among the total 12 studies, five showed insignificant results for hydrocortisone (two) and methylprednisolone (three), while others reported significant results. This systematic review suggested that oral/intravenous corticosteroids might confer clinical benefits in the management of COVID-19, particularly in reducing mortality and severe disease outcomes. However, further investigation was needed to establish standardized protocols regarding dosage, duration, and safety considerations to optimize efficacy and minimize potential adverse effects.

Keywords: efficacy, corticosteroid, SARS-CoV-2, randomized controlled trial, clinical trial

Introduction

The global outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, is associated with significant public health challenges worldwide. The rapid spread and ability to cause a wide spectrum of diseases has raised deep concern globally. The disease was declared a pandemic by the World Health Organization (WHO),[1] and by September 2024, the total number of infected patients exceeded 776 million people.[2] Along with ongoing efforts to develop effective vaccines and antiviral therapies, intensive investigations have been directed toward understanding the optimal clinical management of infected patients.[3–5] In this context, corticosteroids have become a focus of attention due to their anti-inflammatory and immunosuppressive potential.[6–9]

The use of corticosteroids in treating COVID-19 has been the focus of debate since the beginning of the pandemic.[10] These drugs are effective in treating various lung disorders, including conditions such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[11] Conversely, the administration can lead to adverse effects such as prolonged viral clearance, elevated blood sugar levels, and susceptibility to opportunistic infections.[12–14]

Received: 27 June 2024
Accepted: 19 September 2024
Published: 1 October 2024

Several clinical trial studies regarding corticosteroids for COVID-19 have been initiated and reported, including the RECOVERY Clinical Trial. It states that the use of dexamethasone compared with usual care reduces mortality by 28 days in patients who require oxygen therapy or mechanical ventilation.[15] The WHO on September 2, 2020, recommended corticosteroids for the treatment of COVID-19.[16] Although several clinical and observational studies have been conducted to evaluate the effects in infected patients, these results are often inconsistent, leading to uncertainty in clinical practice. Decisions regarding corticosteroid use are also influenced by factors such as disease severity, stage of infection, and patient risk profile, adding complexity to establishing an optimal treatment strategy.[10]

In this context, conducting a systematic review can provide more comprehensive insight into the use of corticosteroids in COVID-19 patients. This study aimed to conduct a comprehensive systematic review of existing literature regarding the use of oral/intravenous (IV) corticosteroids for the treatment of COVID-19. This systematic review consolidates and critically evaluates the existing evidence on corticosteroids use in treating COVID-19, addressing various clinical outcomes such as mortality rates, the need for mechanical ventilation, and length of hospital stay. By focusing exclusively on RCT involving oral/IV corticosteroids and excluding studies combining these treatments with other drugs (except for the Standard of Care (SoC) for COVID-19), this review minimizes potential bias, ensuring that the findings reflect the effects of corticosteroids alone. The synthesis of data from numerous studies identifies trends, research gaps, and clinical implications, offering insights for healthcare professionals and guiding future research in optimizing COVID-19 treatment protocols.

Method

This systematic review was conducted by the Cochrane Handbook for Systematic Reviews of Interventions[17] and the guidelines provided by the York Centre for Reviews and Dissemination (CRD).[18] The report adhered to the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19]

Search Strategy

A systematic search was conducted throughout January 2024, using strategies to identify relevant studies on MEDLINE, Scopus, and Cochrane databases. During this search, original studies meeting the defined criteria were identified. Boolean operators such as "OR" and "AND" were used to expand the exploration within each concept and refine the results, respectively. Additionally, Medical Subject Headings (MeSH) terms were also applied and the detailed search terms are outlined in Table 1. Supplementary manual searches were also performed in healthcare journals and Google Scholar,[17,20] as well as citation chasing by tracing articles in the reference lists.[17]

Table 1 Search Strategy in Database Searching

Database	Search Terms
MEDLINE	("COVID-19"[MeSH Terms] OR "SARS-CoV-2"[MeSH Terms] OR "COVID-19"[Title/Abstract]) AND ("corticosteroid"[Title/Abstract] OR "dexamethasone"[Title/Abstract] OR "dexamethasone"[MeSH Terms] OR "hydrocortisone"[MeSH Terms] OR "hydrocortisone"[Title/Abstract] OR "prednisone"[Title/Abstract] OR "prednisone"[MeSH Terms] OR "prednisolone"[MeSH Terms] OR "prednisolone"[Title/Abstract] OR "betamethasone"[Title/Abstract] OR "betamethasone"[MeSH Terms]) AND "randomized controlled trial"[Publication Type]
Scopus	(COVID-19 OR " SARS-CoV-2") AND (corticosteroid OR dexamethasone OR hydrocortisone OR prednisone OR prednisolone OR betamethasone) AND ((randomized AND controlled AND trial) OR (randomized AND controlled AND trial))
Cochrane	((MeSH descriptor: [COVID-19] explode all trees) OR SARS-CoV-2) AND ((MeSH descriptor: [Adrenal Cortex Hormones] explode all trees) OR (MeSH descriptor: [Dexamethasone] explode all trees) OR (MeSH descriptor: [Hydrocortisone] explode all trees) OR (MeSH descriptor: [Prednisone] explode all trees) OR (MeSH descriptor: [Methylprednisolone] explode all trees) OR (MeSH descriptor: [Prednisolone] explode all trees) OR (MeSH descriptor: [Betamethasone] explode all trees) OR ((corticosteroid): ti, ab, kw) OR ((dexamethasone): ti, ab, kw) OR ((hydrocortisone): ti, ab, kw) OR ((prednisone): ti, ab, kw) OR ((methylprednisolone): ti, ab, kw) OR ((prednisolone): ti, ab, kw) OR ((betamethasone): ti, ab, kw))

Study Selection

All search results were exported to Zotero version 6.0.13 (Corporation for Digital Scholarship, Vienna, USA) and checked for duplicates. The screening process was carried out in two stages, namely initial screening based on title and abstracts followed by full-text screening. Two reviewers (IRL and FR) performed both screening processes. The inclusion criteria included studies published from 2019–2024 with randomized controlled trial (RCT) designs, focused on the use of systemic corticosteroid (oral/IV) in COVID-19 patients aged 18 years old and above, with either standard of care (SoC) plus placebo or SoC plus corticosteroid, and assessed any clinical outcome of patients. On the other hand, RCT studies that did not use a placebo as a control group including efficacy or dose comparisons between corticosteroid class drugs were excluded. RCTs focused on the efficacy of corticosteroid combinations with other drugs were also excluded. Certain studies were excluded to maintain the integrity and clarity of the findings. The exclusion of non-placebo-controlled studies ensures that the comparisons are made between corticosteroid treatment and SoC, eliminating confounding variables and providing a clearer assessment of corticosteroid efficacy. By not including studies that compare different corticosteroid drugs, the review maintains its focus on the general efficacy of corticosteroids as a class, rather than on individual formulations or dosages. Additionally, studies using combined treatments with other drugs, beyond the standard of care, were excluded to avoid confounding effects from other medications. This ensures that any observed outcomes can be attributed solely to corticosteroids, providing a more accurate and unbiased evaluation of their efficacy in treating COVID-19. Protocol articles, conference proceedings, review articles, and non-English studies were excluded. In addition, discrepancies were resolved through collaborative discussion.

Data Extraction

Data were manually extracted into a predetermined format using Microsoft® Excel® 2019 MSO version 2210 (Microsoft Corporation, Redmond, WA, USA) by two independent reviewers (IRL and FR). Discrepancies were resolved through collaborative discussion and in cases of incomplete data, efforts were made to contact corresponding authors through email. Extracted data included various parameters, including author details, publication year, corticosteroid type, country, sample size, patient characteristics, study design, and outcomes.

Risk of Bias

Two reviewers (IRL and FR) assessed the risk of bias, using the JADAD score to evaluate the quality of individual articles. This scoring system comprised three key assessment domains: randomization, blinding method, and participant withdrawal. Scores range from 1 (indicating poor quality) to 5 (reflecting good quality), offering a concise and comprehensive method for assessing the methodological rigor of each study.[21] Discrepancies were resolved through discussion with other reviewers.

Data Synthesis

Descriptive statistics were used to delineate the features of the incorporated studies. A narrative synthesis approach was adopted given the significant methodological diversity. The synthesis entailed thorough discussions in validating results and adhering to the principles outlined by the York Centre for Reviews and Dissemination (CRD) for systematic reviews.[18]

Results

This study identified 108, 1492, and 309 studies from MEDLINE, Scopus, and Cochrane databases, respectively, with one additional study from manual searching. A total of 210 studies were duplicates and four were retracted, leaving only 1.695 to be screened. Furthermore, 1.613 studies were excluded due to the failure to meet the inclusion criteria. A total of 71 did not use a placebo (for control) but instead compared the dose and efficacy of each corticosteroid drug, as well as a combination with other drugs. Finally, 12 RCT studies were included in this systematic review as shown in the flowchart in Figure 1. A complete summary of the results is presented in Table 2.

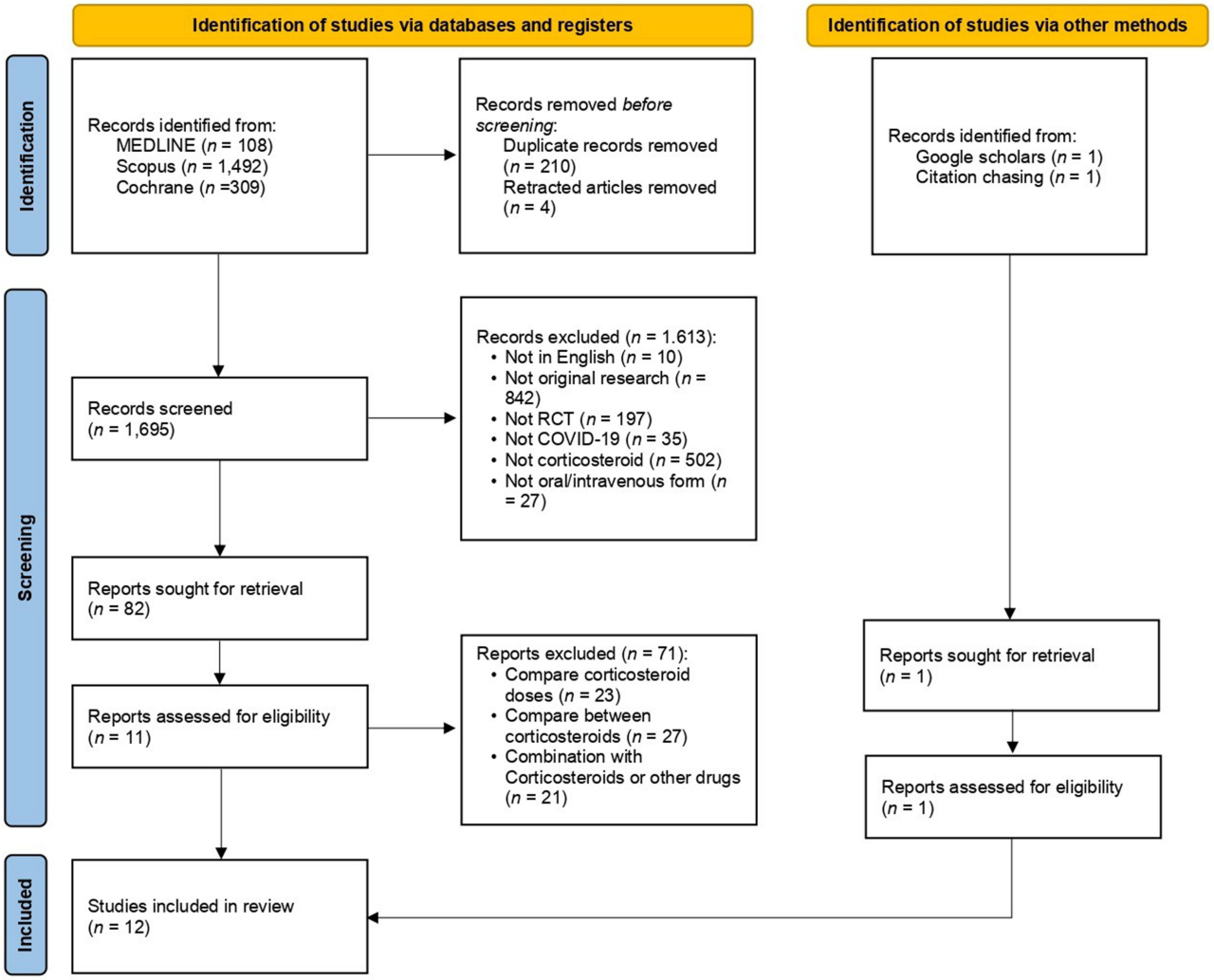

Figure 1 The flowchart of study selection process.

Quality Assessment of the Included Studies

Assessing the quality of studies evaluating the efficacy of medical intervention is crucial, particularly when these studies serve as evidence for treatment choices.[21] Based on the results, a total of six studies achieved a perfect score of 5 points.[26,28,30–33] All included studies had a detailed description of randomization methods, blinding, and description of withdrawal/dropout. However, one study did not contain a description of withdrawal/dropout.[25] The lowest score of JADAD was 3, attributed to the use of a single-blind method and/or absence of explanation regarding the blinding method or withdrawal/dropout description.[22–24,27,29] The implementation of randomization and blinding techniques is essential to ensure data quality and produce reliable results, specifically in clinical trial studies.[21] Table 3 summarizes in detail the risk of bias based on the JADAD Score.

Discussion

The results of this systematic review illustrate that oral/IV corticosteroids are effective against COVID-19, although only two corticosteroids—dexamethasone and methylprednisolone—show significant results. The patient characteristics, doses, and outcomes used in each study vary, preventing a general conclusion.[34,35]

Table 2 Summary of the Efficacy of Oral/Intravenous Corticosteroid Use in COVID-19 Patients

Author	Types of Corticosteroids	Country	Sample Size	Patient Characteristic	Administration	Design Study		Outcomes
						Intervention Group	Control Group	
[22]	Dexamethasone 1	Iran	50 patients (control group: 25; intervention group: 25)	Age > 18 years, mild to moderate acute respiratory distress syndrome (ARDS) due to COVID-19	IV	SoC + dexamethasone 20 mg/day from day 1– 5 and then 10 mg/day from day 6–10.	SoC + placebo	Primary outcomes: • The need for invasive mechanical: not significant • Death rate: not significant Secondary outcomes • Length of hospital stay: not significant • **Length of stay in the intensive care unit (ICU) (p<0.001): control group (7 days); intervention group (3 days)** • Sequential Organ Failure Assessment (SOFA) score: not significant
[23]	Dexamethasone 2 (CoDEX)	Brazil	299 patients (control group: 148; intervention group: 151)	Age > 18 years, moderate to severe ARDS admitted to the ICU	IV	SoC + dexamethasone 20mg IV once daily for 5 days, followed by 10 mg IV once daily for an additional 5 days or until ICU discharge	SoC	Primary outcomes: • **Ventilator-free days (p= 0.04): control group 4 days; intervention group 6,6 days** Secondary outcomes • Clinical status of patients at day 15 using a 6-point ordinal scale: not significant • Mechanical ventilation duration: not significant • **SOFA scores (p= 0.004): control group 7.5; intervention group 6.1** • ICU-free days at 28 days: not significant
[24]	Dexamethasone 3 (RECOVERY)	United Kingdom	6425 patients (control group: 4321; intervention group: 2104)	Age > 18 years with either clinically suspected or laboratory-confirmed SARS-CoV-2 infection, and lacking any medical history deemed by the attending clinician to pose a substantial risk if engaged in the trial	Oral and IV	SoC + oral or IV dexamethasone 6 mg once daily for up to 10 days or until hospital discharge	SoC	Primary outcomes: • **Mortality at 28 days (p<0.001): control group (25,7%); intervention group (22,9%)** Secondary outcomes • Duration of hospitalization: not significant • Invasive mechanical ventilation or death: not significant

(*Continued*)

https://doi.org/10.2147/JEP.S484596 DovePress

Table 2 (Continued).

Author	Types of Corticosteroids	Country	Sample Size	Patient Characteristic	Administration	Design Study		Outcomes
						Intervention Group	Control Group	
[25]	Hydrocortisone 1 (COVID STEROID)	Denmark	30 patients (control group: 14; intervention group: 16)	Age > 18 years with confirmed SARS-CoV-2 infection and severe hypoxia (use of mechanical ventilation or supplementary oxygen with a flow of at least 10 L/min).	IV	SoC + IV hydrocortisone 200 mg for 7 days or until hospital discharge	SoC + placebo	Primary outcomes: • Days alive without the use of life support at day 28: not significant Secondary outcomes • The number of serious adverse reactions: not significant • All-cause mortality at day 28 and 90: not significant • Days alive without life support at day 90: not significant • Days alive and out of the hospital at day 90: not significant
[26]	Hydrocortisone 2 (CAPECOD)	France	149 patients (control group: 73; intervention group: 76)	Age > 18 years admitted to ICUs for acute respiratory failure who had a biologically confirmed or suspected COVID-19.	IV	SoC + hydrocortisone IV 200mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days	SoC + placebo	Primary outcomes: • Treatment failure on day 21: not significant Secondary outcomes: • Cumulative incidences (until day 21) of prone position sessions, extracorporeal membrane oxygenation, and inhaled nitric oxide: not significant • Nosocomial infection on day 28: not significant

[27]	Methylprednisolone 1 (GLUCOCOVID)	Spain	64 patients (control group: 29; intervention group: 35)	Aged ≥18 years, receiving oxygen without mechanical ventilation, and with evidence of systemic inflammatory response	IV	SOC + methyl-prednisolone IV 40mg bid for 3 days followed by 20mg bid for 3 days	SoC	Primary outcomes • Composite endpoint that included in-hospital all-cause mortality with intention-to-treat (ITT) analysis: not significant • **Risk of experiencing the composite endpoint with Per Protocol (PP) analysis (p= 0.043): patients on intervention group had a significantly lower risk of experiencing the composite endpoint** Secondary outcomes • **The variation of the laboratory biomarkers between baseline and 6 days after inclusion: The C-reactive protein (CRP) levels were lower in both groups 6 days later. The decrease was more pronounced in the intervention group (77% decrease vs 43%, p= 0.034).**
[28]	Methylprednisolone 2	China	86 patients (control group: 43; intervention group: 43)	Age ≥ 18 years, laboratory-confirmed SARS-CoV-2 infection and had pneumonia confirmed by chest computed tomography, and diagnosed with COVID-19 pneumonia	IV	SoC + methyl-prednisolone 1 mg/kg per day dissolved in 100 mL 0.9% normal saline was administered IV for 7 days.	SoC + placebo	Primary outcomes: • Clinical deterioration 14 days after randomization: not significant Secondary outcomes: • Clinical cure 14 days after randomization: not significant • Time from randomization to clinical cure: not significant • ICU admission: not significant • Hospitalization duration: not significant • In-hospital mortality: not significant • **Time from virus shedding of SARS-CoV-2 (p= 0.030): control group (8 days); intervention group (11 days)**

(*Continued*)

https://doi.org/10.2147/JEP.S484596

Table 2 (Continued).

Author	Types of Corticosteroids	Country	Sample Size	Patient Characteristic	Administration	Design Study		Outcomes
						Intervention Group	Control Group	
[29]	Methylprednisolone 3	Iran	68 patients (control group: 34; intervention group: 34)	Aged ≥ 18 years, confirmed COVID-19 with SpO2 <90%, elevated CRP (>10 mg·L−1) and interleukin-6 (IL-6) (>6 pg·mL−1) at the early pulmonary phase of the disease before connecting to the ventilator and intubation	IV	SoC+ methyl-prednisolone pulse (intravenous injection, 250 mg/day for 3 days)	SoC	Primary outcomes: • Time of clinical improvement (p=0.011): control group (16.44 days); intervention group (11.84 days) • Time to event (discharge or death) (p=0.006): control group (17.61 days); intervention group (11.62 days)

[30]	Methylprednisolone 4 (TICS-COV19)	Egypt	754 patients (control group: 377; intervention group: 377)	Aged ≥ 18 years, confirmed COVID-19 clinically, radiologically, and by Real Time Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2 of mild or moderate severity with an elevated inflammatory marker CRP, lactate dehydrogenase [LDH], or ferritin).	IV	Mild Case: SoC + methyl-prednisolone 15 mg daily for 1 week, then reduced gradually over 2 weeks. Moderate case: methyl-prednisolone 30 mg daily for 1 week, then reduced gradually over 2 weeks.	SoC	Primary outcomes
								• **The composite endpoint (need for O2, need for hospitalization or 28-day mortality) (p= 0.004): control group 18.67 %); intervention group (11.14%)**
								Secondary outcomes:
								• **Time-to-return to daily activity (p< 0.001): control group (22 days); intervention group (8 days)**
								• **Change in severity (p< 0.001): control group (18.7%); intervention group (11.1 %)**
								• Inflammatory markers course on day 10
								  ○ CRP: not significant
								  ○ Ferritin: not significant
								  ○ **D-dimer (p< 0.001): control group (0.83); intervention group (0.61)**
								  ○ **LDH (p< 0.001): control group (297.5); intervention group (226.3)**

[31]	Methylprednisolone 5	Italy	301 patients (control group: 150; intervention group: 151)	Recent-onset COVID-19 pneumonia, requiring supplemental oxygen in any delivery mode, except invasive mechanical ventilation, with arterial oxygen tension (PaO2)/ inspiratory oxygen fraction (FiO2) between 100 mmHg and 300 mmHg, and CRP>5 mg·dL−1.	IV	SoC + methyl-prednisolone IV 1 gr for 3 consecutive days	SoC + placebo	Primary outcomes: • Duration of patient hospitalization: not significant Secondary outcomes: • Survival free from invasive ventilation with orotracheal intubation: not significant • Overall survival: not significant

[32]	Methylprednisolone 6 (Metcovid)	Brazil	393 patients (control group: 199; intervention group: 194)	Aged ≥ 18 years, had clinical and/or radiological suspicion of COVID-19 (history of fever and any respiratory symptom) and either had SpO2 ≤ 94% with room air, required supplementary oxygen, or required Intermittent Mandatory Ventilation (IMV)	IV	SoC + methyl-prednisolone 0.5 mg/kg	SoC + placebo	Primary outcomes:
								• 28-days mortality: not significant
								Secondary outcomes:
								• Early mortality
								  ○ 7 days: not significant
								  ○ 14 days: not significant
								• The need for orotracheal intubation
								  ○ Day 5: not significant
								  ○ Day 7: not significant
								• The proportion of patients with an oxygenation index (PaO2/FiO2) < 100 by day 7: not significant

[33]	Methylprednisolone 7 (CORTIVID)	Spain	71 patients (control group: 37; intervention group: 34)	Aged ≥ 18 years; cycle threshold (Ct) ≥ 35; presented with symptoms compatible with COVID-19 for at least 7 days; and had at least one of the following: CRP >60 mg/L, IL-6 > 40 pg/ml, or ferritin >1,000 μg/L.	IV	SoC + IV methyl-prednisolone 120mg/day	SoC + placebo	Primary outcomes • Treatment failure at 14 days: not significant Secondary outcomes • Mortality at 28 days: not significant • ICU admission at 28 days: not significant • Need for high-flow oxygen therapy: not significant • Radiological worsening: not significant • Length of hospital stay: not significant

Note: Bold text is for significant outcomes.

https://doi.org/10.2147/JEP.S484596

Table 3 Quality Assessment by JADAD Score

Author	Randomization	Description of randomization	Double-blind method	Description of the blinding method	Description of withdrawal/ drop-out	Total Score
[22]	1	1	1	0	0	3
[23]	1	1	0	1	0	3
[24]	1	1	0	0	1	3
[25]	1	1	1	1	0	4
[26]	1	1	1	1	1	5
[27]	1	1	0	0	1	3
[28]	1	1	1	1	1	5
[29]	1	1	0	1	0	3
[30]	1	1	1	1	1	5
[31]	1	1	1	1	1	5
[32]	1	1	1	1	1	5
[33]	1	1	1	1	1	5

Oral/Intravenous Corticosteroids Used for COVID-19

Corticosteroids have been extensively used in the treatment of conditions related to COVID-19, such as SARS, MERS, severe influenza, and community-acquired pneumonia.[12,14,36,37] Their ability to reduce systemic inflammation and prevent respiratory failure has made them a central component in treating severe COVID-19.[38,39] Among the corticosteroids used, oral and intravenous dexamethasone, hydrocortisone, and methylprednisolone are the most common.

RCT Findings: Population, Dosage, and Outcomes Variations

Several randomized controlled trials (RCTs) have investigated the efficacy of corticosteroids, especially dexamethasone, for treating COVID-19. The RECOVERY trial, one of the largest studies with over 6000 participants, showed that dexamethasone reduced mortality among patients receiving mechanical ventilation.[24] However, this benefit was less significant in those requiring only supplemental oxygen and absent in patients not requiring respiratory support.[24] The large sample size in RECOVERY strengthens the robustness of its findings, but other trials, such as smaller studies of hydrocortisone, faced challenges in interpreting results due to its adaptive design and relatively smaller sample size.

Among the three studies on dexamethasone,[40] two (Dexamethasone 1 and 2) used the same dosage regimen (20 mg/day for days 1–5, followed by 10 mg/day for days 6–10) but reported different patient characteristics and clinical outcomes.[22,23] Dexamethasone 1 involved patients with disease severity mild to moderate and reported the length of stay (LOS) in ICU as the significant outcome—intervention vs control group LOS were 3 days vs 7 days ($p < 0.001$).[22] On the other hand, Dexamethasone 2 involved patients with moderate to severe conditions and reported ventilator-free days (control group 4 days, intervention group 6.6 days) and SOFA score (control group 7.5, intervention group 6.1) as the significant outcomes ($p = 0.04$).[23] In Dexamethasone 3, the dosage regimen was 6 mg/day for 10 days[22,23] and the patients' characteristics were those with critically ill COVID-19 on mechanical ventilation.[22–24] The outcome with significant results ($p < 0.001$) was the mortality rate at 28 days, where the control was 25.7% and the intervention group was 22.9%.[24] However, concerns have arisen regarding the generalizability of these trials due to differences in study designs and the populations studied. This variation may influence outcomes, particularly when considering the timing and stage of the diseases at which corticosteroids are administered.

Besides dexamethasone, hydrocortisone was also used as an alternative treatment for critically ill COVID-19 patients. Two studies reported hydrocortisone use for severe COVID-19 patients who already required mechanical ventilators.[25,26] The dose used for the first 7 days of treatment was the same at 200 mg/day. For Hydrocortisone 1, the dose was continued until the patient was discharged,[25] while for Hydrocortisone 2, the dose decreased to 100 mg/day for 4 days and 50 mg/day for 3 days, in a total of 14 days.[26] The two studies measured different outcomes, for example, Hydrocortisone 1 measured days alive without life support at day 28 as the primary outcome, whereas Hydrocortisone 2 measured

treatment failure at day 21. However, both studies did not report significant results. In contrast, a prospective meta-analysis showed that hydrocortisone when compared with usual care reduced the risk of death by about a third.[41]

Methylprednisolone is another corticosteroid that has shown potential in mitigating excessive immune response in COVID-19 patients.[42] Seven studies on methylprednisolone also showed variations in the population involved, dosage regimen, and outcomes yielded. For Methylprednisolone 1, the patients involved were receiving oxygen without mechanical ventilation, along with a dose of 40 mg for 3 days followed by 20mg for 3 days.[27] The study showed significant results in the risk of experiencing the composite endpoint with Per Protocol (PP) analysis—where patients on methylprednisolone had a significantly lower risk of experiencing the composite endpoint (p = 0.043)—and in the variation of the laboratory biomarkers between baseline and 6 days after inclusion—where the CRP levels were lower in both groups 6 days later and the decrease was more pronounced in the methylprednisolone group (77% versus 43%, p = 0.034).[27] For Methylprednisolone 2, the participants were COVID-19 patients with pneumonia, treated using a methylprednisolone dose of 1 mg/kg per day. Significant results were only in the outcome time from virus shedding of SARS-CoV-2 (p = 0.030) as follows: control group (8 days); intervention group (11 days).[28] Severely hospitalized patients with confirmed COVID-19 at the early pulmonary phase were involved in Methylprednisolone 3 study, with the dose used 250 mg/day for 3 days. The significant results reported were in the time of clinical improvement (p=0.011) including control (16.44 days) and intervention group (11.84 days) and the time to event (discharge or death) (p=0.006) in control (17.61 days) and intervention group (11.62 days).[29] Methylprednisolone 4 was used for mild and moderate patients with a dose of 15 mg (mild) and 30 mg (moderate) daily for 1 week, then reduced gradually over 2 weeks. The results obtained for the primary outcome showed a significant difference in the composite endpoint (need for O_2, and hospitalization or 28-day mortality) (p = 0.004); including the control (18.67%) and intervention group (11.14%). Significant differences were also shown in the secondary outcome, such as time-to-return to daily activity ($p < 0.001$): control group (22 days), intervention group (8 days) as well as change in severity (p<0.001): control group (18.7%), intervention group (11.1%). Inflammatory markers course at day 10 was only significantly different in D-dimer and LDH, but not in CRP and Ferritin.[30] Methylprednisolone 5, 6, and 7 involved different population characteristics and dosage regimens, and also measured different outcomes.[31–33] However, all of them did not show significant results in the outcomes measured.[31–33]

Most studies (n = 4) on methylprednisolone showed promising effects on clinical outcomes, although some studies did not. Variations in dosing regimens and patient/population profiles could explain these discrepancies. For instance, studies using higher doses of methylprednisolone tended to show more significant outcomes. The variations in the studies also suggest that the optimal dose for corticosteroid treatment may depend on the severity of the patient's condition and the timing of intervention. A similar finding was also confirmed in a meta-analysis by Hasan et al, which found that high-dose methylprednisolone therapy can be a promising alternative in the treatment of severely ill COVID-19 patients.[43]

This study found that dexamethasone and methylprednisolone showed good results across all levels of COVID-19 severity, including mild, moderate, and severe cases. Both dexamethasone and methylprednisolone have been studied more extensively than other corticosteroids. A meta-analysis comparing the efficacy of methylprednisolone and dexamethasone indicated that methylprednisolone significantly decreased plasma ferritin and the neutrophil/lymphocyte ratio in severe cases compared to dexamethasone.[44] Additionally, methylprednisolone at a dose of 2 mg/kg/day showed a better prognosis than dexamethasone. Regarding mortality, when only RCT studies were considered, methylprednisolone significantly reduced mortality compared to dexamethasone.[44] Several systematic reviews and meta-analyses on the use of corticosteroids for COVID-19 patients have also been conducted. Overall, most systematic reviews measure mortality, and the results indicate that corticosteroids reduce patient mortality compared to the control group, particularly in studies using the RCT method.[6,45,46] However, some studies did not show significant results for mortality outcomes, especially when including other study methods such as cohort and multi-center studies.[45,47]

Mechanism of Corticosteroids Related to COVID-19

The utilization of corticosteroids has become a primary strategy for many clinicians in managing hospitalized COVID-19 patients, particularly those with severe manifestations. In such cases, patients often experience hyperinflammation due to an exaggerated immune response to viral invasion. This hyperinflammation commonly affects the respiratory tract,

leading to symptoms such as dyspnea.[34] This condition frequently contributes to mortality in COVID-19 patients by precipitating respiratory failure and reducing oxygen supply to critical organs.[35]

Corticosteroids function as immunosuppressive agents, mitigating excessive inflammatory responses and preventing the progression of hyperinflammation.[48] At a molecular level, corticosteroids are posited to indirectly affect SARS-CoV -2 by inhibiting the inflammatory processes triggered by the virus.[49] Upon infection, SARS-CoV-2 infiltrates host cells through interactions with angiotensin-converting enzyme-2 (ACE-2) receptors, initiating an immune response.[50] This activation triggers the release of cytokines in large quantities, resulting in a "cytokine storm".[51] In COVID-19 infections, cytokines such as interleukins (IL-1, IL-2, IL-6, IL-8, dan IL-12) and interferons (INF-α, INF-β, dan INF-γ) play a significant role in recruiting immune cells including macrophages and lymphocytes.[52] Corticosteroids suppress the activation and recruitment of these immune cells through their immunosuppressive effects, thereby preventing the deleterious effects of cytokine storms that can lead to dyspnea, multi-organ failure, and death.[53] A more detailed elucidation of corticosteroid mechanisms is shown in Figure 2.

However, the immunosuppressive properties of corticosteroids also raise concerns about impairing the body's ability to clear viruses, potentially prolonging infections.[13,54] The suppression of inflammation must be balanced with the risk of viral replication, as over-suppressing the immune response—particularly in the early stages of infection—could allow viral loads to increase. Therefore, both the timing and dosage of corticosteroid therapy are crucial. In severe cases with significant inflammation, corticosteroids are generally recommended by the clinical guidelines because their benefits in controlling inflammation outweigh the risks of potential viral replication.[55]

Additionally, variability in cytokine responses among different patient populations influences the effectiveness of corticosteroid therapy. Factors such as age, comorbidities, and genetic predisposition contribute to the intensity and composition of cytokine storms.[56,57] Older adults and those with underlying conditions like obesity or diabetes, tend to exhibit more robust inflammatory responses, which makes them more likely to benefit from corticosteroid treatment, while younger or healthier individuals may not.[58,59] Therefore tailoring corticosteroids to each patient based on their inflammatory profile and disease severity is critical for optimizing outcomes and minimizing risks.

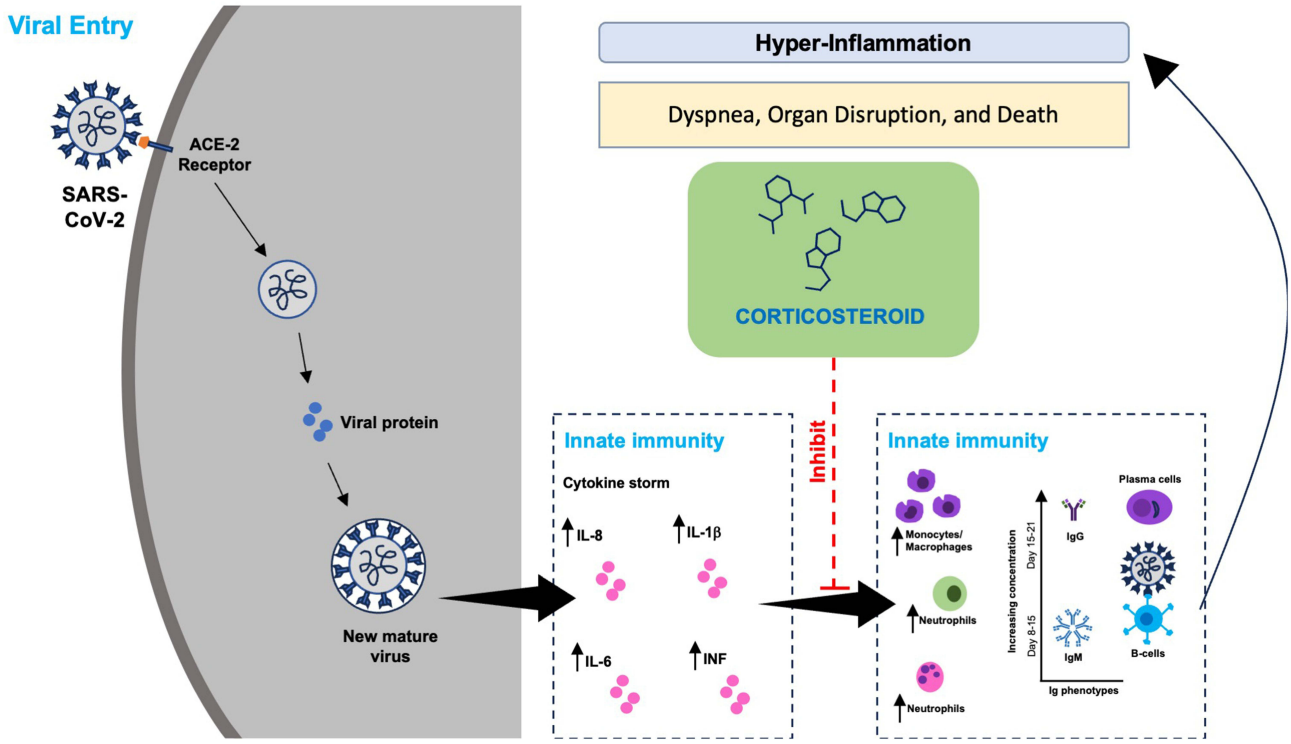

Figure 2 Possible mechanism of action of corticosteroid against COVID-19 infection.

Comparing Corticosteroids with Other Immunosuppressive Agents

While corticosteroids have been widely used, other immunosuppressive agents such as monoclonal antibodies or Janus Kinase (JAK) inhibitors have been explored. Besides their higher cost and limited availability, these agents offer more targeted suppression of inflammatory pathways. For instance, tocilizumab, an IL-6 inhibitor, has shown promise in reducing cytokine storm effects without the broad immunosuppression seen with corticosteroids. However, the broader action of corticosteroids may offer an advantage in rapidly evolving, severe conditions where multiple inflammatory pathways are activated. While newer agents may be more specific and reduce immune-related side effects, corticosteroids remain the frontline treatment due to their accessibility and broad efficacy. In addition, RCTs have not yet demonstrated the superiority of these agents over corticosteroids, especially in settings where resources are limited.

Pros and Cons of Using Corticosteroids for COVID-19

The widespread adoption of corticosteroids as a therapeutic intervention in managing COVID-19 patients has been supported by a comprehensive examination of various factors within the clinical landscape. A central aspect of this consensus is the recognition that patients showing severe disease manifestations often present with a distinctive laboratory profile characterized by a paradoxical phenomenon. Despite the severity of symptoms, the viral load tends to be disproportionately low, particularly in the presence of cytokine storms.[60,61] This observation underscores the potency of the host's hyperimmune response, which effectively curtails the viral burden within the body. Therefore, conventional therapeutic strategies focusing solely on antiviral interventions are gradually replaced by a distinct approach aimed at mitigating the adverse consequences of excessive inflammation.

In this context, corticosteroids have become crucial therapeutic agents, leveraging potent immunomodulatory properties to temper the hyperactivity of the immune system and mitigate tissue damage.[62] The pragmatic appeal of corticosteroid therapy also extends to economic feasibility. Dexamethasone in particular is widely accessible and has a relatively modest cost, rendering it an accessible option for healthcare systems globally.[63] Moreover, the versatile modes of administration, including both local and systemic routes, afford clinicians the flexibility to tailor treatment regimens to suit individual patient needs.[64]

The prominence of dexamethasone in the COVID-19 therapeutic landscape is underscored by a strong body of clinical evidence, with crucial trials such as the RECOVERY study elucidating the efficacy in reducing mortality rates.[24] In the landmark trial entailing a sizable cohort, oral or IV administration of dexamethasone at a specific dosage regimen yielded tangible benefits, such as a significant decline in mortality rates by the 28th day of treatment. Pharmacoeconomic analyses further corroborate the favorable profile of dexamethasone, demonstrating cost-effectiveness with an Incremental Cost-Effectiveness Ratio (ICER) of $5208 per Quality-Adjusted Life Year (QALY).[65]

This favorable cost-benefit proposition is in contrast to remdesivir, which is associated with substantially higher costs, resulting in a less favorable ICER of $384,412.8 per QALY.[65] Therefore, within the intricate tapestry of COVID-19 therapeutics, corticosteroids, epitomized by dexamethasone, have the advantage of clinical efficacy, economic prudence, and therapeutic versatility, offering significant benefits in the relentless battle against the pandemic.

While corticosteroids have demonstrated significant benefits in managing COVID-19, it is essential to address the potential risks associated with their long-term use and the increased likelihood of secondary infections. On the positive side, corticosteroids leverage their potent immunomodulatory properties to temper the hyperactivity of the immune system, effectively reducing mortality rates and improving clinical outcomes in severe cases. They are also widely accessible and cost-effective compared to some newer treatments, making them a practical option for healthcare systems. However, prolonged corticosteroid therapy can lead to adrenal suppression, making patients more susceptible to infections and complicating recovery. As corticosteroids suppress the immune response, patients may experience an increased risk of secondary infections, including bacterial and fungal infections, with studies indicating heightened rates of ventilator-associated pneumonia among corticosteroid-treated patients. Additionally, individuals with chronic conditions requiring long-term corticosteroid treatment may experience complications such as osteoporosis, hypertension, and hyperglycemia, further compounding the risks associated with COVID-19. A cohort study conducted in the United States on 19,973 subjects, reported that corticosteroid use in patients not requiring oxygen therapy was associated with an increased risk of mortality, with a hazard ratio of 1.76.[66] Furthermore, corticosteroid administration has been associated

with elevated risks of hyperglycemia in patients, with a 22% and 14% increase observed in high and low-dose regimens respectively.[67] It is also important to recognize the potential deleterious effects of corticosteroids on patients at high risk of fungal infections. Previous studies found an 11% heightened risk of fungal infections among COVID-19 patients receiving dexamethasone.[68] These results underscore the necessity of a comprehensive risk-benefit assessment before initiating corticosteroid therapy to ensure patient safety.

Real-world data have also provided valuable insights into corticosteroid use beyond controlled settings. Einarsdottir et al show that patients receiving glucocorticoid (GC) treatment before COVID-19 infection face excess mortality, primarily due to complications such as sepsis, pulmonary embolism, and severe COVID-19 symptoms. Corticosteroids impair the immune response, making it difficult for the body to combat SARS-CoV-2 and increasing vulnerability to secondary infections like sepsis. Additionally, these patients have a higher likelihood of requiring ICU admission and face an elevated risk of death, underscoring the need for careful evaluation of long-term corticosteroid use in individuals with chronic conditions, especially during acute viral infections.[69]

Aside from the direct risks associated with corticosteroid administration, careful consideration must also be given to the timing of therapy initiation.[28] In early-stage patients, corticosteroid administration may prove detrimental, as high viral loads may still be present, potentially precipitating viremia.[70] Therefore, diligent assessment of viral load is important before deciding on corticosteroid therapy initiation.

Strength, Limitations, and Practical Implication

This study offers a comprehensive comparison of the effects of multiple corticosteroids, including dexamethasone, hydrocortisone, and methylprednisolone, on COVID-19 outcomes. It provides a balanced view by integrating both large-scale trials like RECOVERY and smaller, more nuanced studies. It highlights the importance of sample size, study design, and dose variations in shaping outcomes. The study's strength is reinforced by the fact that the RCTs reviewed were mostly of high quality, which enhances the reliability of the findings.

Despite its strength, this study has several limitations. First, the variability in study design such as sample size and patient characteristics, dosing regimens, and outcomes measured across the included RCTs complicate the generalizability and consistency of the evidence. Second, the study relies heavily on data from trials and may not fully capture real-world complexities, such as the impact of comorbid conditions, long-term side effects, and patient adherence to treatment protocols. Third, the study's focus on RCTs may overlook observational data and pragmatic trials that provide insights into the corticosteroids' real-world effectiveness, safety, and long-term outcomes. Finally, the study only focused on patients aged 18 years or older. This limits the applicability of the findings to pediatric populations, who may respond differently to corticosteroid treatment due to variations in immune system development and disease progression.

Future research is needed to establish optimal dosing regimens, particularly for patients at higher risk of adverse effects. Studies accounting for the complexities of patients' comorbidities, long-term side effects, and adherence to treatment protocol will help bridge the gap between controlled trial environments and practical clinical settings. Incorporating observational data and pragmatic trials can offer valuable perspectives on the real-world effectiveness and safety of corticosteroids, complementing RCT findings. Future research should include pediatric populations to better understand the distinct immune responses and treatment effects in younger patients, ensuring that findings are applicable across all age groups. This broader approach would enhance the understanding of corticosteroid use and its long-term implications in COVID-19 patients. Studies could also focus on comparing the efficacy and cost-effectiveness of corticosteroids with its alternatives. Comparative studies on efficacy, safety, long-term outcomes, and cost across different patient populations and dosing strategies are needed to refine treatment protocols and expand therapeutic options for COVID-19 while considering healthcare resource allocation.

The findings underscore the importance of a balanced approach in corticosteroid therapy for COVID-19, particularly in balancing short-term benefits with long-term risks. Clinicians should consider patient-specific factors such as age, comorbidities, and disease severity, and closely monitor patients on long-term corticosteroid therapy to mitigate risks such as secondary infections, hyperglycemia, and mortality. Clinicians must also carefully consider the dosage and timing of corticosteroid administration, particularly in early-stage patients with high viral loads, to optimize patient outcomes.

Conclusion

In conclusion, this systematic review highlights the effectiveness of oral/IV corticosteroids, particularly dexamethasone and methylprednisolone, in treating COVID-19 patients aged 18 years or older, although the evidence varies across different trials and patient groups. Clinicians should carefully weigh the benefits of corticosteroids against potential risks, such as long-term side effects and increased susceptibility to infections. Personalized treatment plans that consider dosage, timing, and patient-specific factors are critical for optimizing outcomes.

Acknowledgments

The authors would like to thank the Rector of Universitas Padjadjaran for facilitating the APC via the Directorate of Research and Community Engagement.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med*. 2020;382(10):929–936. doi:10.1056/NEJMOA2001191
2. COVID-19 cases | WHO COVID-19 dashboard. Available From: https://data.who.int/dashboards/covid19/cases. Accessed September 7, 2024.
3. Li G, Hilgenfeld R, Whitley R, De Clercq E. Therapeutic strategies for COVID-19: progress and lessons learned. *Nat Rev Drug Discov*. 2023;22(6):449–475. doi:10.1038/s41573-023-00672-y
4. Latarissa IR, Barliana MI, Meiliana A, et al. Efficacy of quinine sulfate in patients with mild-to-moderate COVID-19: A randomized controlled trial. *Indo Biomed J*. 2023;15(6):366–374. doi:10.18585/INABJ.V15I6.2543
5. Latarissa IR, Meiliana A, Sormin IP, et al. The efficacy of herbal medicines on the length of stay and negative conversion time/rate outcomes in patients with COVID-19: a systematic review. *Front Pharmacol*. 2024;15:1383359. doi:10.3389/FPHAR.2024.1383359
6. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care*. 2020;24(1). doi:10.1186/S13054-020-03400-9
7. Villar J, Confalonieri M, Pastores SM, Umberto Meduri G. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. *Crit Care Explor*. 2020;2(4):E0111. doi:10.1097/CCE.0000000000000111
8. Alijotas-Reig J, Esteve-Valverde E, Belizna C, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: a comprehensive review. *Autoimmun Rev*. 2020;19(7):102569. doi:10.1016/J.AUTREV.2020.102569
9. Jiang S, Liu T, Hu Y, et al. Efficacy and safety of glucocorticoids in the treatment of severe community-acquired pneumonia: a meta-analysis. *Medicine*. 2019;98(26). doi:10.1097/MD.0000000000016239
10. Mattos-Silva P, Felix NS, Silva PL, et al. Pros and cons of corticosteroid therapy for COVID-19 patients. *Respir Physiol Neurobiol*. 2020;280:103492. doi:10.1016/J.RESP.2020.103492
11. Lee KH, Yoon S, Jeong GH, et al. Efficacy of corticosteroids in patients with SARS, MERS and COVID-19: a systematic review and meta-analysis. *J Clin Med*. 2020;9(8):1–17. doi:10.3390/JCM9082392
12. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757–767. doi:10.1164/RCCM.201706-1172OC/SUPPL_FILE/DISCLOSURES.PDF
13. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395(10223):473–475. doi:10.1016/S0140-6736(20)30317-2
14. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):1525–1531. doi:10.1371/JOURNAL.PMED.0030343
15. Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with covid-19 – preliminary report. *medRxiv*. 2020;2020. doi:10.1101/2020.06.22.20137273
16. Clinical management of COVID-19. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19/. Accessed March 15, 2024.
17. Cochrane handbook for systematic reviews of interventions | cochrane training. Available from: https://training.cochrane.org/handbook. Accessed March 18, 2024.
18. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *Lancet Infect Dis*. 2010;10(4):226. doi:10.1016/s1473-3099(10)70065-7
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021:372. doi:10.1136/BMJ.N71
20. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Syst Rev*. 2017;6(1):1–12. doi:10.1186/S13643-017-0644-Y/TABLES/5
21. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12. doi:10.1016/0197-2456(95)00134-4
22. Jamaati H, Hashemian SMR, Farzanegan B, et al. No clinical benefit of high dose corticosteroid administration in patients with COVID-19: a preliminary report of a randomized clinical trial. *Eur J Pharmacol*. 2021;897:173947. doi:10.1016/J.EJPHAR.2021.173947

23. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307–1316. doi:10.1001/JAMA.2020.17021
24. Horby P, Lim WS, Emberson J, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693–704. doi:10.1056/NEJMOA2021436
25. Munch MW, Meyhoff TS, Helleberg M, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: the COVID STEROID randomised, placebo-controlled trial. *Acta Anaesthesiol Scand*. 2021;65(10):1421–1430. doi:10.1111/AAS.13941
26. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically Ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298–1306. doi:10.1001/JAMA.2020.16761
27. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: an open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr*. 2021;133(7–8):303–311. doi:10.1007/S00508-020-01805-8
28. Tang X, Feng YM, Ni JX, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. *Respiration*. 2021;100(2):116–126. doi:10.1159/000512063
29. Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J*. 2020;56(6):2002808. doi:10.1183/13993003.02808-2020
30. Issak ER, Amin MM. Timing of corticosteroids in non-severe non-hospitalized COVID-19 patients: open-label, two-center, randomized controlled study (TICS-COV19 study). *Korean J Intern Med*. 2023;38(2):207–217. doi:10.3904/KJIM.2022.232
31. Salvarani C, Massari M, Costantini M, et al. Intravenous methylprednisolone pulses in hospitalised patients with severe COVID-19 pneumonia: a double-blind, randomised, placebo-controlled trial. *Eur Respir J*. 2022;60(4):2200025. doi:10.1183/13993003.00025-2022
32. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): a Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. *Clin Infect Dis*. 2021;72(9):E373–E381. doi:10.1093/CID/CIAA1177
33. Les I, Loureiro-Amigo J, Capdevila F, et al. Methylprednisolone pulses in hospitalized COVID-19 patients without respiratory failure: a randomized controlled trial. *Front Med*. 2022:9. doi:10.3389/FMED.2022.807981
34. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–513. doi:10.1016/S0140-6736(20)30211-7
35. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. doi:10.1001/JAMA.2020.1585
36. Lansbury L, Rodrigo C, Leonardi-Bee J, Nguyen-Van-tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Emergencias*. 2021;33(6):466–467. doi:10.1002/14651858.CD010406.PUB3/MEDIA/CDSR/CD010406/IMAGE_N/NCD010406-CMP-001-03.PNG
37. Siemieniuk RAC, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(7):519–528. doi:10.7326/M15-0715
38. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids — new mechanisms for old drugs. **N Engl J Med**. 2005;353(16):1711–1723. doi:10.1056/NEJMRA050541
39. Corticosteroids for COVID-19. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed March 15, 2024.
40. Romanou V, Koukaki E, Chantziara V, et al. Dexamethasone in the treatment of COVID-19: primus inter pares? *J Pers Med*. 2021;11(6):556. doi:10.3390/JPM11060556
41. Sterne JAC, Murthy S, Jv. D, et al. Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330–1341. doi:10.1001/JAMA.2020.17023
42. El-Saber Batiha G, Al-Gareeb AI, Saad HM, Al-kuraishy HM. COVID-19 and corticosteroids: a narrative review. *Inflammopharmacology*. 2022;30(4):1189. doi:10.1007/S10787-022-00987-Z
43. Hasan SS, Kow CS, Mustafa ZU, Merchant HA. Does methylprednisolone reduce the mortality risk in hospitalized COVID-19 patients? A meta-analysis of randomized control trials. *Expert Rev Respir Med*. 2021;15(8):1049–1055. doi:10.1080/17476348.2021.1925546
44. Hong S, Wang H, Li S, Liu J, Qiao L. A systematic review and meta-analysis of glucocorticoids treatment in severe COVID-19: methylprednisolone versus dexamethasone. *BMC Infect Dis*. 2023;23(1). doi:10.1186/S12879-023-08280-2
45. Ebrahimi Chaharom F, Pourafkari L, Ebrahimi Chaharom AA, Nader ND. Effects of corticosteroids on Covid-19 patients: a systematic review and meta-analysis on clinical outcomes. *Pulm Pharmacol Ther*. 2022;72:102107. doi:10.1016/J.PUPT.2021.102107
46. Pulakurthi YS, Pederson JM, Saravu K, et al. Corticosteroid therapy for COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2021;100(20):e25719. doi:10.1097/MD.0000000000025719
47. Tlayjeh H, Mhish OH, Enani MA, et al. Association of corticosteroids use and outcomes in COVID-19 patients: a systematic review and meta-analysis. *J Infect Public Health*. 2020;13(11):1652–1663. doi:10.1016/J.JIPH.2020.09.008
48. Yang JW, Yang L, Luo RG, Xu JF. Corticosteroid administration for viral pneumonia: COVID-19 and beyond. *Clin Microbiol Infect*. 2020;26(9):1171–1177. doi:10.1016/J.CMI.2020.06.020
49. Isidori AM, Arnaldi G, Boscaro M, et al. COVID-19 infection and glucocorticoids: update from the Italian society of endocrinology expert opinion on steroid replacement in adrenal insufficiency. *J Endocrinol Invest*. 2020;43(8):1141–1147. doi:10.1007/S40618-020-01266-W
50. Shirbhate E, Pandey J, Patel VK, et al. Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention. *Pharmacol Rep*. 2021;73(6):1539–1550. doi:10.1007/S43440-021-00303-6
51. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, et al. COVID-19 infection: an overview on cytokine storm and related interventions. *Virol J*. 2022;19(1). doi:10.1186/S12985-022-01814-1
52. Mcmahon JH, FRACPA U, Anton FCICM, Peleg Y. Remdesivir for the treatment of Covid-19 — preliminary report. **N Engl J Med**. 2020;383(10):992–994. doi:10.1056/NEJMC2022236
53. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: a systemic review and a clinician's perspective. *Diabetes Metab Syndr*. 2020;14(5):971. doi:10.1016/J.DSX.2020.06.054

54. Langarizadeh MA, Tavakoli MR, Abiri A, Ghasempour A, Rezaei M, Ameri A. A review on function and side effects of systemic corticosteroids used in high-grade COVID-19 to prevent cytokine storms. *EXCLI J*. 2021;20:339. doi:10.17179/EXCLI2020-3196
55. Corticosteroids for COVID-19. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed September 7, 2024.
56. Saal M, Loeffler-Wirth H, Gruenewald T, Doxiadis I, Lehmann C. Genetic Predisposition to SARS-CoV-2 Infection: cytokine Polymorphism and Disease Transmission within Households. *Biology*. 2023;12(11):1385. doi:10.3390/BIOLOGY12111385/S1
57. Zhang JJ, Dong X, Liu GH, Gao YD. Risk and protective factors for COVID-19 morbidity, severity, and mortality. *Clin Rev Allergy Immunol*. 2023;64(1):90–107. doi:10.1007/S12016-022-08921-5
58. Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). *Diabetes Metab Res Rev*. 2021;37(2). doi:10.1002/DMRR.3377
59. Landstra CP, de Koning EJP. COVID-19 and diabetes: understanding the interrelationship and risks for a severe course. *Front Endocrinol*. 2021;12. doi:10.3389/FENDO.2021.649525
60. Meyerowitz EA, Sen P, Schoenfeld SR, et al. Immunomodulation as treatment for severe coronavirus disease 2019: a systematic review of current modalities and future directions. *Clin Infect Dis*. 2021;72(12):E1130–E1143. doi:10.1093/CID/CIAA1759
61. Sharma A, Ahmad Farouk I, Lal SK. COVID-19: a review on the novel coronavirus disease evolution, transmission, detection, control and prevention. *Viruses*. 2021;13(2):202. doi:10.3390/V13020202
62. Cruciani M, Pati I, Masiello F, Pupella S, De Angelis V. Corticosteroids use for COVID-19: an overview of systematic reviews. *Infez Med*. 2022;30(4):469. doi:10.53854/LIIM-3004-1
63. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):1–25. doi:10.1186/1710-1492-9-30/TABLES/11
64. Ko JJ, Wu C, Mehta N, Wald-Dickler N, Yang W, Qiao R. A comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. *J Intensive Care Med*. 2021;36(6):673–680. doi:10.1177/0885066621994057
65. Carta A, Conversano C. Cost utility analysis of remdesivir and dexamethasone treatment for hospitalised COVID-19 patients - a hypothetical study. *BMC Health Serv Res*. 2021;21(1). doi:10.1186/S12913-021-06998-W
66. Crothers K, DeFaccio R, Tate J, et al. Dexamethasone in hospitalised COVID-19 patients not on intensive respiratory support. *Eur Respir J*. 2022;60(1):2102532. doi:10.1183/13993003.02532-2021
67. Abbass H, Abbott A, Abbott A, et al. Higher dose corticosteroids in patients admitted to hospital with COVID-19 who are hypoxic but not requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2023;401(10387):1499–1507. doi:10.1016/S0140-6736(23)00510-X
68. Søvik S, Barrat-Due A, Kåsine T, et al. Corticosteroids and superinfections in COVID-19 patients on invasive mechanical ventilation. *J Infect*. 2022;85(1):57–63. doi:10.1016/J.JINF.2022.05.015
69. Einarsdottir MJ, Kirui BK, Li H, et al. Impact of chronic oral glucocorticoid treatment on mortality in patients with COVID-19: analysis of a population-based cohort. *BMJ Open*. 2024;14(3):e080640. doi:10.1136/BMJOPEN-2023-080640
70. Bahl A, Johnson S, Chen NW. Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients. *Intern Emerg Med*. 2021;16(6):1593–1603. doi:10.1007/S11739-021-02655-6