Corticosteroid use in COVID-19 patients: A systematic review and meta-analysis on clinical outcomes

Judith van Paassen  
Leids Universitair Medisch Centrum

Jeroen S. Vos  
LUMC department of intensive care

Eva M. Hoekstra  
Leids Universitair Medisch Centrum

Katinka M.I. Neumann  
Leids Universitair Medisch Centrum

Pauline C. Boot  
Leids Universitair Medisch Centrum

Sesmu M. Arbous (marbous@lumc.nl)  
Leids Universitair Medisch Centrum  https://orcid.org/0000-0001-5242-3257

Research

Keywords: COVID-19, SARS-CoV-2, coronavirus, corticosteroids, mortality, viral clearance, mechanical ventilation

Posted Date: November 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-52240/v2

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License

Version of Record: A version of this preprint was published on December 14th, 2020. See the published version at https://doi.org/10.1186/s13054-020-03400-9.
Abstract

Background: In the current SARS-CoV-2 pandemic, there has been worldwide debate on the use of corticosteroids in COVID-19. In the recent RECOVERY trial, evaluating the effect of dexamethasone, a reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation was shown. Their results have led to considering amendments in guidelines or actually already recommending corticosteroids in COVID-19. However, the effectiveness and safety of corticosteroids still remain uncertain, and reliable data to further shed light on the benefit and harm are needed.

Objectives: The aim of this systematic review and meta-analysis was to evaluate the effectiveness and safety of corticosteroids in COVID-19.

Methods: A systematic literature search of RCTS and observational studies on adult patients was performed across Medline/PubMed, Embase, and Web of Science from 1st of December 2019 until 1st of October 2020, according to the PRISMA guidelines. Primary outcomes were short-term mortality and viral clearance (based on RT-PCR in respiratory specimens). Secondary outcomes were: need for mechanical ventilation, other oxygen therapy, length of hospital stay and secondary infections.

Results: Forty-four studies were included, covering 20,197 patients. In twenty-two studies, the effect of corticosteroid use on mortality was quantified. The overall pooled estimate (observational studies and RCTs) showed a significant reduced mortality in the corticosteroid group (OR 0.72 (95%CI 0.57-0.87). Furthermore, viral clearance time ranged from 10-29 days in the corticosteroid group and from 8-24 days in the standard of care group. Fourteen studies reported a positive effect of corticosteroids on need for and duration of mechanical ventilation. A trend towards more infections and antibiotic use was present.

Conclusions: Our findings from both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality and a reduction of need for mechanical ventilation. And although data in the studies were too sparse to draw any firm conclusions, there might be a signal of delayed viral clearance and an increase in secondary infections.

Background

Since the start of the outbreak, Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus SARS-CoV-2, has spread globally from Wuhan, China. 40,559,736 cases have been reported and 1,121,499 people have died as of October 19th.[1] Many countries have been affected, causing immense stress on healthcare systems worldwide. This is the third epidemic caused by a coronavirus, after Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012.[2,3] The clinical presentation ranges from asymptomatic or mild disease to severe pneumonia in which the most severe cases deteriorate with acute respiratory distress syndrome (ARDS) requiring prolonged mechanical ventilation, or even Extracorporeal Membrane Oxygenation (ECMO).[4,5] Approximately 16-35% develop severe pneumonia, 2-17% need mechanical ventilation, of whom up to 15 % need ECMO therapy,[6,7,8] and the case fatality rate is 1.4-15%.[5, 9, 10] In the pathophysiology of severe COVID-19, the host immune response plays a key role and it has become evident that COVID-19 pneumonia is associated with both hyper inflammation and immunoparalysis.[11] A clinical presentation of massive vascular inflammation, disseminated coagulation, shock, and ARDS is frequently triggered.[9-11]

Though many therapies aiming at mitigation of the inflammatory response are being evaluated, strong evidence of benefit is lacking. Corticosteroids might have beneficial effects in overcoming both hyperinflammation and ARDS.[4,15-17] Furthermore, they could serve as an easily accessible and affordable treatment option. On the other hand, there are known adverse effects of corticosteroid use, such as delayed viral clearance, opportunistic infections and suppression of the hypothalamic-pituitary-adrenal axis.[2,18,19] Earlier studies done in MERS-CoV and SARS-CoV showed delayed viral clearance, opportunistic infections and hyperglycemia.[20-22] Therefore, a high number of observational studies and randomized controlled trials (RCT) on corticosteroids for COVID-19 have been initiated and reported, and the signal is a beneficial effect. The RECOVERY trial was the first to report that the use of dexamethasone as opposed to usual care reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation.[23] And a prospective meta-analysis of seven randomized clinical trials showed that administration of corticosteroids was associated with lower 28-day all-cause mortality. [24] And while initially the World Health Organization (WHO) recommended against corticosteroid treatment, as of September 2nd 2020, the WHO recommends systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical COVID-19. [15, 25] Also, the Surviving Sepsis Guideline on management of COVID-19 recommends administration of steroids in patients with severe COVID-19 on mechanical ventilation with ARDS, and in patients with COVID-19 and refractory shock.[26]
However, the effectiveness and safety of corticosteroids still remain uncertain, because of scarcity of RCTs and inconclusive observational studies, and reliable data to further shed light on the benefit and harm are needed. Therefore the aim of this systematic review and meta-analysis of observational studies and RCTs was to evaluate the effectiveness and safety of corticosteroids in COVID-19.

**Methods**

**Data sources and search strategy**

A systematic review according to the PRISMA guidelines was conducted.[27] The meta-analysis was retrospectively registered under number 38752 at ISRCTN.org. A comprehensive systematic search was conducted for published studies in Medline/PubMed, Embase, and Web of Science from December 1st 2019 to October 1st 2020. The search strategy consisted of the components "COVID-19", "intensive care", and "corticosteroids" (Appendix 1).

**Eligibility**

RCTs and observational cohort studies assessing the effect of corticosteroids in COVID-19 were eligible if they met the following inclusion criteria: adult patients (age ≥ 18 years), COVID-19 patients diagnosed by reverse transcriptase polymerase chain reaction (RT-PCR), reporting on outcome measures in relation to corticosteroid treatment, corticosteroids not restricted for type, dose and duration. Studies concerning pregnant women or children, reviews, case series including less than 15 patients and articles that were not available in English were excluded.[28]

**Definition of primary and secondary outcomes**

The primary outcomes were mortality (i.e short-term mortality as defined in the study, including 28-day, 30-day and hospital mortality) and viral clearance (i.e. as defined by the study, based on RT-PCR in respiratory specimens). Secondary outcomes were: need for invasive mechanical ventilation, duration of mechanical ventilation, ventilator free days or other oxygen therapy as reported by the investigators, length of hospital stay (LOS-hospital) and secondary infections. For exact used definitions see Appendix 2.

**Study selection**

Suitable studies were selected in two stages. First, six independent reviewers screened all selected titles and abstracts (JvP, JV, EH, KN, PB, SA). If there was consensus that a study was unsuitable for inclusion, it was excluded. Next, the full-text articles were screened independently by two authors and included if both authors agreed. If needed, the article was discussed with the third reviewer until consensus was reached.

**Data extraction and quality analysis**

After selection, data were extracted by one and checked by a second investigator (JvP, JV, EH, KN, PB). For each study, the author, journal, country, city and hospital in which the study was conducted, date of start of inclusion, study population, study groups, type, dose, route of administration of corticosteroid, median time before corticosteroid initiation, duration of administration, primary and secondary outcomes and adverse events at any time point after admission were extracted in a standardized data extraction form (Appendix 2).

For each individual study the quality was assessed. For RCTs the Risk of Bias was assessed on six domains (random sequence generation, concealment of allocation, blinding, selective outcome reporting, incomplete outcome data and other).[29,30] The Newcastle Ottawa Scale was used for validity assessment of observational studies.[31,32] The NOS score ranges from 0 (low quality) to 9 (high quality) points.

**Data analysis and reporting**

For the effect of corticosteroids on mortality, a pooled estimate was calculated and graphically summarized in a forest plot. Data from observational studies were analyzed separately from the RCTs, and both separate results and overall combined outcomes were calculated and summarized in the plot. When available, the adjusted odds ratio (OR), relative risk (RR) from the cohort studies were used for pooling to reduce confounding. Since the endpoint (mortality) occurred relative infrequently, the OR will be close to the RR and therefore we decided to pool both RR and OR estimates of the individual studies.[33] Furthermore, a pooled estimate was calculated and graphically summarized in a forest plot for need for mechanical ventilation.
To allow studies to have a different underlying effect, a random effects model was used. $I^2$ statistics was used to quantify heterogeneity. Furthermore, for the pooled estimate of effect on mortality, $\tau^2$ was used to assess the variance of the true effects. The GRADE approach was used to assess the quality of the evidence for the effect of corticosteroids on mortality. STATA 16.0 was used to perform data analysis.

**Results**

**Study selection**

Our search yielded 1640 unique studies. After qualification of title and abstract, 101 studies were selected for full review. Based on exclusion criteria, 57 additional studies were excluded (references in Appendix 3). The remainder of 44 studies, comprising 20,197 patients, was included in this systematic review and meta-analysis. (Figure 1)

**Study Characteristics (table 1 and Appendix 4)**

Thirty-one of the 44 studies originated in China, 11 in Europe, five in North America, two in South America and one study was multi-continental. The inclusion period ranged from late December 2019 until August 20, 2020. The majority of studies were retrospective observational studies (37/44), five were RCTs [23, 34-37], and there were two studies with historical controls [38, 40]. The study population varied from hospitalized patients (28/44) to patients admitted to the Intensive Care Unit (ICU) (15/44), and one study included discharged patients for viral clearance assessment. The median age of patients ranged from 34 to 75 years.

For the observational studies the median NOS score was 5 (2-8) points (Appendix 5). For the RCT the risk of bias table is depicted in Figure 2.

**Corticosteroid Regimen (table 1 and Appendix 6)**

In the 44 studies very diverse corticosteroid strategies were used. If reported (n=35), methylprednisolone was the most frequently prescribed (n = 28) [35,36,38-65]. Prednisone (n=5) and dexamethasone (n=5) and hydrocortisone (n=4) were also used, some in studies that allowed multiple corticosteroid regimens (n=9).

The indication to start corticosteroids was described in 12 studies (Appendix 6): in three studies corticosteroids were started at diagnosis/hospital admission. [38,41,56] In five studies ICU admission or respiratory deterioration were the indications to start, either randomized according to study protocol [23,34,35,37] or not randomized [38,48, 49,60,64].

In 29 studies the dose of corticosteroids was reported: In 16 studies an equivalent dose of > 1 mg/kg prednisolone was used [37-39,41,43,44,48-51,53,54,56-58,64] and in 11 studies a lower equivalent dose than 1 mg/kg prednisolone [23,34-36,40,42,47,52,62,63,65].

In two studies a low and high dose group were present [45,46]. The duration of therapy varied within a range of 5-10 days, in observational studies frequently dependent on clinical condition of patients.

**Effect of steroids on primary and secondary outcomes (table 2, Appendix 7)**

Thirty-five of 44 studies reported on Mortality. Thirteen of these could not be integrated in the meta-analysis due to only overall mortality reporting (n=5), [45,63,64,66,67] or only descriptive reporting (n=8), i.e. of a trend towards better outcome (n=3), [42,68,69], no effect (n=3) [44,49,65] or negative effect on outcome (n=2) [50,52]. For the remainder of 22 studies, a pooled estimate was calculated and graphically summarized in a forest plot (figure 2). The mortality reported in these studies was mainly 28-day mortality (11 studies), in 6 studies in-hospital mortality of shorter duration, and in 5 studies unreported (see Appendix 7). The overall risk estimate (OR) was 0.72 (95%CI 0.57-0.87), suggesting a beneficial effect of steroids use in COVID-19 patients hospitalized with moderate or severe respiratory failure on mortality. Studies were heterogeneous (overall $I^2$ of 51.1%, p= 0.002) with a between-study variance ($\tau^2$) of 0.048. For the subset of RCTs the risk estimate was 0.84 (95%CI 0.72-0.96) and $I^2$ and $\tau^2$ were 31.2% (p= 0.213) and 0.0096, corresponding to less heterogeneity and less between-study variance.

Thirteen from 44 studies reported on viral clearance, which most frequently was defined as two consecutive negative RT-PCR on nasopharyngeal swabs, or a cycle time value of 40 or more. In the corticosteroid group viral clearance time ranged from 5 to 29 days, in the standard of care group from 8 to 24 days. In nine of 13 studies viral shedding was delayed in the corticosteroid group. [40,43,46,47,53,59,63, 65,70]. In the other four studies, viral clearance was equal (n=2) [50,71] or even better in the corticosteroid group.
(n=2) [44,52]. The numbers are too small to quantify the effect of corticosteroids on viral shedding, or to compare viral shedding time in subgroups of severity of COVID illness, dose, type or timing of corticosteroids administered. (Appendix 8)

In twelve studies length of hospital stay was compared in both corticosteroid and non-corticosteroid groups. The outcomes varied between studies: six reported longer hospital stay in the corticosteroid group [36,47,53,56,66] and five reported the opposite [23,34,38,52,54] or no effect on hospital stay [58].

Fourteen of 17 studies reported a positive effect of corticosteroids on ventilator free days [34,37,56], on the number of patient requiring mechanical ventilation for respiratory insufficiency [23,35,38,48,54,57,58,60,68,72] or on the time on ventilator [52]. In the pooled analyses fewer patients required mechanical ventilation in the corticosteroids group (RR 0.71 (95%CI 0.54-0.97) (Figure 3) though only seven studies supplied sufficient data for this analysis. Jeronimo and Keller failed to demonstrate significant differences [36,73] and one study reported the opposite effect.[53] The dose of corticosteroids could not be related to respiratory outcomes.

Eleven studies reported on the effect of corticosteroids on oxygenation. Various definitions were used: liters per minute of oxygen needed, oxygen saturation, PaO2/FiO2 ratio. The effect of corticosteroids on oxygenation was very heterogeneous: In four studies there was no significant effect [41,42,51,55], in three studies significant improvement was described [50,60,64] and in four studies worse outcome was observed. [35,39,54,57]

Six studies addressed secondary infections. More frequently broad spectrum antibiotics were used in de corticosteroid group [39,47,53] and more secondary infections/sepsis episodes were described [35,36]. Only Tomazini found a lower percentage of secondary infections in the corticosteroid group. A dose effect of steroids of development of infections/antibiotic need could not be demonstrated.

Discussion

In this systematic review and meta-analysis on effectiveness and safety of corticosteroids in COVID-19 patients, the pooled estimate of the observational retrospective studies and the RCTs supported the positive effect of corticosteroids therapy on mortality in CoVID-19 disease as reported in the RECOVERY trial. [23] Furthermore, in already respiratory compromised COVID-19 patients, the need for mechanical ventilation was lower in corticosteroid treated COVID-19 patients. And although data in the studies were too sparse to draw any firm conclusions, there might be a signal of delayed viral clearance and an increase in antibiotic use and infections in the corticosteroid group. However, this did not seem to lead to prolonged hospital stay or increased mortality.

Besides reviews extrapolating knowledge on SARS-CoV or MERS-CoV [21] or on non-viral ARDS [4], or combining studies on SARS-CoV or MERS-CoV [2,18,74], to our knowledge, only three other meta-analyses on this subject were conducted with conflicting results. [24,75,76] Sarkar et al. found low-quality evidence with high variability that in patients with COVID-19 the steroids may be associated with an around twofold increase in mortality [75]. Tlayjeh et al.[76] found no significant difference in mortality or mechanical ventilation need, at the cost of a prolonged viral clearance time. The investigators explained that the discordance in studies was due to bias in the large number of non-RCTs. In the third, very robust, prospective meta-analysis of published and pending trials (inclusion has pretty much stopped since the Recovery trial was published), Sterne et al.[24], found that in critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality. A downside of this rather robust study was that almost 60 percent of the population consisted of the Recovery study population and a reasonable amount of data was generated from unpublished, unfinished studies.

Compared to these other systematic reviews on corticosteroids and COVID-19, ours was able to include the largest number of studies and COVID-19 patients. Furthermore, we included both observational studies and RCTs to be able to assess adverse effects such as viral clearance and risk of infections. To obtain the highest possible quality, we excluded non-peer reviewed pre-published manuscripts and furthermore, if available, we included adjusted estimates in the meta-analysis, reducing bias by incongruent study groups.

Our review has several limitations. Most of the included studies were retrospective cohort studies with increased risk of bias and lower level of evidence, as we confirmed by the GRADE classification (Table 2, Appendix 10). Besides that, large heterogeneity in the studies was present (i.e. study population, type, dose, initiation and duration of corticosteroids, outcome measures) and we emphasize that definitions of primary and secondary outcome measures varied greatly and pooled data from this review should be interpreted cautiously. However, we tried to narrow down the outcome measure to short-term mortality. Furthermore, we decided to carefully note the applied definition in the studies in our data extraction tables and include only outcomes as defined by the investigators if they were appropriate for our study, i.e. 28-day or closely related short-term in-hospital mortality. We agree that this variation in definition is indeed a drawback of this review. And although the pooled data from this review should therefore be interpreted cautiously, they represent the
effect of corticosteroids on short-term 28-day mortality and the pooled estimates for RCTs, and adjusted and unadjusted observational studies pointed towards the same direction, i.e. of a beneficial effect. In many studies confounding by indication was evidently present: two studies described that corticosteroid administration was “at the discretion of the treating physician”[40,41] and four reported that severe patients were more likely to receive corticosteroid treatment. [40,49,60,66] Many studies had incomplete follow-up and a considerable amount of patients did not reach definite endpoints. However, our conscious exclusion of non-peer-reviewed studies, the focus on a measurable and quantifiable endpoint, and, if possible, inclusion of risk estimates corrected for confounders and propensity matched, increased the validity of the retrospective evidence supporting the RECOVERY trial. Furthermore, from the included studies, 26 originated in China, with 13 from the hot spot regions (Wuhan, Hubei, Shanghai). This might impair generalizability but although overlapping study populations were present within the included studies (see table in Appendix 4.), this was only incidentally the case for secondary outcome measures. For the main outcome multiple publication bias was unlikely. (Appendix 11). Furthermore, 42% of the study population was included from outside China. Moreover, in terms of generalizability, the median age from the included patients in this review ranged from 34 to 72 years. However, data from the CDC state that 42.9% of hospitalized patients in the United States are ≥65 years and European numbers from the European Centre for Disease Prevention and Control (ECDC) show that 54.2% hospitalized patients are ≥65 years with great variation between countries.[77,78]. Despite aforementioned limitations, still, this systematic review and meta-analysis confirms the conclusion of the meta-analysis of the RCTs that critically ill COVID-19 patients hospitalized for moderate or severe respiratory failure, with or without mechanical ventilation, should receive corticosteroids.

Severe COVID-19 patients are faced with a twofold problem. On the one hand, there is the hyperinflammatory response, resulting in pulmonary thrombosis, extravasation of cell debris, and acute lung injury or even ARDS.[79] On the other hand there is a need to clear the viral infection itself. This primary phenomenon suggests a possible target for corticosteroids.[17] Thus, the confirmation that there is predominantly a beneficial effect of corticosteroids on mortality is congruent with pathophysiological reasoning and prior knowledge. In our study we found a signal of delayed viral clearance, but data in the studies were too sparse to draw any firm conclusions. Therefore, what is lacking is knowledge on the optimal start of corticosteroid administration after the start of illness, specific subpopulations and type, dose and duration. RCTs so far reported a strongly beneficial effect on mortality but did not investigate optimal timing and indication of corticosteroid administration.[24] and our study wasn't able to provide an answer to the latter issues, either. Therefore, future research should focus on which patient characteristics, laboratory and radiological markers can be used to guide indication and timing of corticosteroid treatment, particularly in relation to safety (e.g. delayed viral clearance, increased incidence of secondary infections).

**Conclusion**

Our findings from both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality and a reduction of the need for mechanical ventilation. And although data in the studies were too sparse to draw any firm conclusions, there might be a signal of delayed viral clearance and an increase in secondary infections related to corticosteroid use. Optimal timing, dose and duration of corticosteroids, in relation to safety, remain subject for further investigation. Since corticosteroids are affordable and easily accessible in healthcare systems quivering under the pressure of the global outbreak of this rapidly spreading coronavirus, this field of research should be a universal priority.

**List Of Abbreviations**

ARDS: acute respiratory distress syndrome

CDC: Centers for Disease Control and Prevention

CI: confidence interval

COVID-19: coronavirus disease 2019

CT: computed tomography

ECDC: European Centre for Disease Prevention and Control

FiO2: inspiratory oxygen fraction

HR: hazard ratio
Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Availability of data and materials
Not applicable

Conflicts of interest
All persons who meet authorship criteria are listed as authors. The manuscript has been seen and approved by all authors. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding
Not applicable

Author contributions
SA created the study project. JvP, JV, PB, EH, KN, and SA extracted and analysed the data. JvP and SA performed the statistical analyses with the aid of OD (in acknowledgements). JvP, PB, EH, KN, and SA wrote the draft and all co-authors critically revised the manuscript.
Acknowledgements

We would like to express our gratitude to C. Pees, librarian, for her efforts in designing the search strategies used in collecting data. We would also like to express our gratitude to Olaf M. Dekkers for his aid in the statistical analysis, i.e. calculating pooled estimate and constructing the forest plots.

References

1. European Centre for Disease Prevention and Control. (Accessed October 14, 2020 at https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases).
2. Li H, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Leukemia. 2020 Jun;34(6):1503-11.
3. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020 Feb 15;395(10223):470-3.
4. Villar J, Confalonieri M, Pastores SM, et al. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. Crit Care Explor. 2020 Apr;2(4):e0111.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-62.
6. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-81.
7. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
8. Ziehr DR, Alladina J, Petri CR, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. American Journal of Respiratory and Critical Care Medicine. 2020;201(12):1560-4.
9. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-4.
10. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The perspectives of clinical immunologists from China. Clin Immunol. 2020 May;214:108393.
11. Aljotas-Reig J, Esteve-Valverde E, Belizia C, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmun Rev. 2020 May;19(7):102567.
12. 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 (Baltimore). 2019 Jun;98(26):e16239.
13. Willar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020 Mar;8(3):267-76.
14. Singh AK, Majumdar S, Singh R, et al. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective. Diabetes Metab Syndr. 2020 Jun;24(14):971-8.
15. Veronese N, Demurtas J, Yang L, et al. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Front Med (Lausanne). 2020;7:170.
16. 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 Mar 15;197(6):575-67.
21. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020 Feb 15;395(10223):473-5.
22. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006 Sep;3(9):e343.
23. Horby R, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020 Jul 17. doi:10.1056/NEJMoA2021436.
24. Sterne JAC, Murthy S, Diaz JV, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020.
25. World Health Organization. (Accessed October 14, 2020 at https://www.who.int/publications/i/item/clinical-management-of-covid-19)
26. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020 May;46(5):854-87.
27. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 Jan 1;4(1):1.
28. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000 Nov;53(11):1119-29.
29. Dekkers OM. Meta-analysis: Key features, potentials and misunderstandings. Res Pract Thromb Haemost. 2018 Oct;2(4):658-63.
30. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011 Oct 18;343:d5928.
31. Coding manual for case-control studies. GA Wells BS, D O'Connell, J Peterson, et al. (Accessed October 18, 2020 at http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf)
32. Newcastle-Ottowa quality assessment scale case control studies. GA Wells BS, D O'Connell, J Peterson, et al. (Accessed at Octobre 18, 2020 at http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf)
33. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997;315:1533–7.
34. Angus DC, Derde L, Al-Beidh F, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317-29.
35. 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):1-9.
36. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase Ib, Placebo-Controlled Trial. Clin Infect Dis. 2020.
37. 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.
38. Fadel R, Morrison AR, Vahia A, et al. Early short course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis. 2020 May 19. doi:10.1093/cid/ciaa601.
39. Bani-Sadr F, Hentzien M, Pascard M, et al. Corticosteroid therapy for patients with COVID-19 pneumonia: a before-after study. Int J Antimicrob Agents. 2020;56(2):106077.
40. Fang X, Mei Q, Yang T, et al. Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19. J Infect. 2020;81(1):147-78.
41. Fernández-Cruz A, Ruiz-Antorán B, Muñoz-Gómez A, et al. A Retrospective Controlled Cohort Study of the Impact of Glucocorticoid Treatment in SARS-CoV-2 Infection Mortality. Antimicrob Agents Chemother. 2020;64(9).
42. Gazzaruso C, Carlo Stella N, Mariani G, et al. Impact of anti-rheumatic drugs and steroids on clinical course and prognosis of COVID-19. Clin Rheumatol. 2020;39(8):2475-7.
43. Gong Y, Guan L, Jin Z, et al. Effects of methylprednisolone use on viral genomic nucleic acid negative conversion and CT imaging lesion absorption in COVID-19 patients under 50 years old. J Med Virol. 2020.
44. Hu Y, Wang T, Hu Z, et al. Clinical efficacy of glucocorticoid on the treatment of patients with COVID-19 pneumonia: A single-center experience. Biomed Pharmacother. 2020;130:110529.
45. Huang H, Song B, Xu Z, et al. Predictors of coronavirus disease 2019 severity: A retrospective study of 64 cases. Jpn J Infect Dis. 2020.
46. Li Q, Li W, Jin Y, et al. Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study. Infectious Diseases and Therapy. 2020.

47. Li S, Hu Z, Song X. High-dose but Not Low-dose Corticosteroids Potentially Delay Viral Shedding of Patients With COVID-19. Clinical Infectious Diseases. 2020.

48. Li Y, Zhou X, Li T, et al. Corticosteroid prevents COVID-19 progression within its therapeutic window: a multicentre, proof-of-concept, observational study. Emerg Microbes Infect. 2020;9(1):1869-77.

49. Liu J, Zheng X, Huang Y, et al. Successful use of methylprednisolone for treating severe COVID-19. J Allergy Clin Immunol. 2020;146(2):325-7.

50. Liu K, Fang Y-Y, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;133(9):1025-31.

51. Lu X, Chen T, Wang Y, et al. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. Critical Care. 2020;24(1):241.

52. Ma Q, Qi D, Deng XY, et al. Corticosteroid therapy for patients with severe novel Coronavirus disease 2019. Eur Rev Med Pharmacol Sci. 2020;24(15):8194-201.

53. Ma Y, Zeng H, Zhan Z, et al. Corticosteroid Use in the Treatment of COVID-19: A Multicenter Retrospective Study in Hunan, China. Frontiers in Pharmacology. 2020;11(1198).

54. Majmundar M, Bansara T, Lenik JM, et al. Efficacy of corticosteroids in non-intensive care unit patients with COVID-19 pneumonia from the New York Metropolitan region. PLoS One. 2020;15(9):e0238827.

55. Mikulska M, Nicolini LA, Signori A, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One. 2020;15(8):e0237831.

56. Nelson BC, Laracy J, Shoucri S, et al. Clinical Outcomes Associated with Methylprednisolone in Mechanically Ventilated Patients with COVID-19. Clin Infect Dis. 2020.

57. Rodríguez-Baño J, Pachón J, Carratalá J, et al. Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: a multicentre cohort study (SAM-COVID-19). Clin Microbiol Infect. 2020.

58. Salton F, Confalonieri P, Meduri GU, et al. Prolonged Low-Dose Methylprednisolone in Patients With Severe COVID-19 Pneumonia. Open Forum Infectious Diseases. 2020;7(10).

59. Shen Y, Zheng F, Sun D, et al. Epidemiology and clinical course of COVID-19 in Shanghai, China. Emerg Microbes Infect. 2020;9(1):1537-45.

60. Wang Y, Jiang W, He Q, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther. 2020;5(1):57.

61. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.

62. Wu J, Huang J, Zhu G, et al. Systemic Corticosteroids and Mortality in Severe and Critical COVID-19 Patients in Wuhan, China. J Clin Endocrinol Metab. 2020;105(12).

63. Xu K, Chen Y, Yuan J, et al. Factors Associated With Prolonged Viral RNA Shedding in Patients with Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2020;71(15):799-806.

64. Yang SS, Lipes J. Corticosteroids for critically ill COVID-19 patients with cytokine release syndrome: a limited case series. Can J Anaesth. 2020;67(10):1462-4.

65. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Med J Aust. 2020;212(9):416-20.

66. Feng Y, Ling Y, Bai T, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020;201(11):1380-8.

67. Wang Z, Yang B, Li Q, et al. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):769-77.

68. Callejas Rubio JL, Luna Del Castillo JD, de la Hera Fernández J, et al. Effectiveness of corticoid pulses in patients with cytokine storm syndrome induced by SARS-CoV-2 infection. Med Clin (Barc). 2020;155(4):159-61.

69. Wang K, Zhang Z, Yu M, et al. 15-day mortality and associated risk factors for hospitalized patients with COVID-19 in Wuhan, China: an ambispective observational cohort study. Intensive Care Medicine. 2020;46(7):1472-4.
70. Chen X, Zhu B, Hong W, et al. Associations of clinical characteristics and treatment regimens with the duration of viral RNA shedding in patients with COVID-19. Int J Infect Dis. 2020;98:252-60.
71. Shi D, Wu W, Wang Q, et al. Clinical Characteristics and Factors Associated With Long-Term Viral Excretion in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection: a Single-Center 28-Day Study. J Infect Dis. 2020;222(6):910-8.
72. Chroboczek T, Lacoste M, Wackenheim C, et al. Corticosteroids in Patients With COVID-19: What About the Control Group? Clinical Infectious Diseases. 2020.
73. Keller MJ, Kitsis EA, Arora S, et al. Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19. J Hosp Med. 2020;15(8):489-93.
74. Yang Z, Liu J, Zhou Y, et al. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020;81(1):e13-e20.
75. Sarkar S, Khanna P, Soni KD. Are the steroids a blanket solution for COVID-19? A systematic review and meta-analysis. J Med Virol. 2020.
76. Tlayjeh H, Mhish OH, Enani MA, et al. Association of corticosteroids use and outcomes in COVID-19 patients: A systematic review and meta-analysis. Journal of Infection and Public Health. 2020.
77. COVID-NET. Centers for Disease Control and Prevention. (Accessed at October 14, 2020 at https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html)
78. European Centre for Disease Prevention and Control. (Accessed at October 14, 2020 at https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html)
79. Polak SB, Van Gool IC, Cohen D, et al. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol. 2020 Jun 22. doi:10.1038/s41379-020-0603-3:1-11.
80. Cao J, Tu WJ, Cheng W, et al. Clinical Features and Short-term Outcomes of 102 Patients with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):748-55.
81. Huang M, Yang Y, Shang F, et al. Clinical characteristics and predictors of disease progression in severe patients with COVID-19 infection in Jiangsu province, China: a descriptive study. Am J Med Sci. 2020;360(2):120-128.
82. Liu J, Zhang S, Wu Z, et al. Clinical outcomes of COVID-19 in Wuhan, China: a large cohort study. Ann Intensive Care. 2020;10(1):99.

**Tables**

**Table 1. Study Characteristics**
| Author          | Reference | Study type         | Type - dose \(\gamma\) corticosteroids | Sample size | CoViD - Study population | Reporting outcome | Quality score (Risk of bias or NOS) | Main findings                                                                                                                                                                                                 |
|-----------------|-----------|--------------------|----------------------------------------|-------------|--------------------------|-------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Angus           | 34        | REMAP\(^{\text{C}}\) | Hydrocortisone < 1 mg/kg ED            | 403         | ICU patients             | x                 | x x x                              | Two hydrocortisone dosing resulted high probabilities of superiority with regard to the odds of improvement in organ support-free days within 21 days, compared to standard of care                                    |
| 2 Bani-Sadr     | 39        | Cohort with historical controls | Prednisolone or Methylprednisolone \(\geq 1\) mg/kg ED | 319 | Hospitalized patients | x x x | 4 | Addition of corticosteroids to our institution’s COVID-19 treatment protocol was associated with a significant reduction in hospital mortality in the ‘after’ period |
| Cao             | 80        | Retrospective Observational | Unknown                               | 102 | Hospitalized patients | x                 | 5 | Patient characteristics seen more frequently in those who died were development of systemic complications following onset of the illness and the severity of disease requiring admission to the ICU.                                      |
| Chen Zu         | 39        | Retrospective Observational | Unknown                               | 267 | Hospitalized patients | x x x | 7 | Corticosteroid treatment is associated with prolonged viral RNA shedding and should be used with caution.                                                                 |
| 5 Chroboczek    | 72        | Retrospective Observational | Unknown                               | 70 | Hospitalized patients | x                 | 6 | Corticosteroids therapy affected the risk of intubation with a risk difference of \(-47.1\%\) (95% CI \(-71.8\) to \(-22.5\)).                                    |
| Dequin          | 35        | Randomized controlled trial | Methylprednisolone or Hydrocortisone < 1 mg/kg ED | 149 | ICU patients with respiratory failure | x x x | Risk of Bias\(^{\text{2}}\) | Low dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21 in critically ill patients.                                |
| Fadel           | 38        | Quasi Experimental | Methylprednisolone \(\geq 1\) mg/kg ED | 213 | Moderate to severe CoViD patients | x x x | 6 | An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care |
|   |   | Study Design | Treatment | Study Population | x | x | x | x | 5 |
|---|---|-------------|-----------|-----------------|---|---|---|---|---|
| 8 | Fang Mei | 40 | Retrospective Observational | Methylprednisolone < 1 mg/kg ED | 78 | Hospitalized patients | x | 5 | Low-dose corticosteroid therapy may not delay viral clearance in patients with COVID-19. |
| 9 | Feng Ling | 66 | Retrospective Observational | Unknown | 476 | Hospitalized patients | x | x | Differences in AT II receptor inhibitors use were associated with different severities of disease. Multiple lung lobes involvement and pleural effusion were associated with the severity of COVID-19. Advanced age (>75 yr) was a risk factor for mortality. |
| 10 | Fernandez | 41 | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED | 463 | Patients with ARDS hyperinflammation | x | x | 5 | Glucocorticoid use is associated with increased survival and improved mortality rates in Severe COVID-19 patients. |
| 11 | Gazzaruso | 42 | Retrospective Observational | Methylprednisolone or Prednisone < 1 mg/kg ED | 219 | Hospitalized patients | x | x | 3 | Anti-rheumatic drugs, probably steroids included, may modulate inflammation and avoid a hyperinflammation that leads to severe complications and death in subjects with COVID-19. |
| 12 | Gong Guan | 43 | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED | 34 | Hospitalized Patients < 50 years | x | x | 6 | Corticosteroids therapy can effectively release COVID-19 symptoms, improve oxygenation, and prevent disease progression. However, it can prolong the negative conversion of nucleic acids. |
| 13 | Horby | 23 | Randomized controlled trial | Dexamethasone < 1 mg/kg ED | 6425 | Hospitalized patients | x | x | Risk of Bias² The use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. |
| 15 | Hu Wang | 44 | Retrospective Observational | Prednisolone or Methylprednisolone ≥ 1 mg/kg ED | 308 | Hospitalized patients | x | x | 4 | Glucocorticoid therapy did not significantly influence the outcomes nor the |
| Study   | Year | Study Design | Intervention                                                                 | Study Groups | Sample Size | Outcome | Risk of Bias | Findings                                                                                                                                 |
|---------|------|--------------|-------------------------------------------------------------------------------|--------------|-------------|---------|--------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Huang Song | 2020 | Retrospective Observational | Methylprednisolone 2 study groups: High: ≥ 1 mg/kg ED Low: < 1 mg/kg ED | Hospitalized patients | x | 64 | | There were no significant differences in the duration of severe illness or the number of days on high level respiratory support between low dose and high dose methylprednisolone group. The mean number of days in the hospital was higher in the high dose group. |
| Huang Yang | 2020 | Retrospective Observational | Unknown | Severe COVID patients | x | 60 | | There were no statistically significant differences in immunoglobulin therapy and GCs therapy between the improvement and deterioration subgroups. |
| Jeronimo | 2020 | Randomized controlled trial | Methylprednisolone < 1 mg/kg ED | Hospitalized patients | x | 393 | | Results showed no overall reduction in mortality in 28 days. Patients over 60 years presented a lower mortality in a subgroup analysis. |
| Keller | 2020 | Retrospective Observational | Unknown | Early hospitalized patients | x | 1806 | | In high CRP group, glucocorticoids show significantly reduced risk of mortality or mechanical ventilation (odds ratio, 0.23; 95% CI, 0.08–0.70). In low CRP group glucocorticoids were associated with significantly increased risk of mortality or mechanical ventilation (OR, 2.64; 95% CI,1.39–5.03). |
| Li Hu | 2020 | Retrospective Observational | Methylprednisolone high and low ED | Hospitalized patients | x | 203 | | A dose response relation is suggested for corticosteroids on viral shedding. In addition, high-dose but not low-dose corticosteroids were found to potentially increase mortality in severe patients |
| Li Li | 2020 | Retrospective Observational | Methylprednisolone or Prednisone < 1 mg/kg ED | Non Severe COVID patients | x | 475 | | Early, low-dose, and short-term corticosteroids therapy was associated with worse clinical outcomes |
|   | Name      | Age | Study Design       | Treatment                                      | Sample Size | Control | Outcome Measure                                      | Authors | Results/Comments                                                                 |
|---|-----------|-----|--------------------|-----------------------------------------------|-------------|---------|-----------------------------------------------------|---------|-----------------------------------------------------------------------------|
| 21| Li Zhou   | 48  | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED                | 187         | x x     | Radiologically progressive CoVID patients           | x x x   | Short-term, low-to-moderate-dose corticosteroids benefits patients with LDH levels of less than two times the ULN, who may be in the early phase of excessive inflammation. |
| 22| Lui Fang  | 49  | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED                | 101         | x       | Hospitalized patients                               |         | The majority of patients present primarily with fever, and typical manifestations on chest imaging. Middle-aged and elderly patients with underlying comorbidities are susceptible to respiratory failure and may have a poorer prognosis. |
| 23| Liu Zhang | 81  | Retrospective Observational | Unknown                                        | 1190        | x       | Hospitalized patients                               |         | Treatment with glucocorticoids increased the risk of progression from not severe to severe disease (OR 3.79, 95% CI 2.39–6.01). |
| 24| Liu Zheng | 50  | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED                | 101         | x x     | Hospitalized patients                               | x x     | Timely and appropriate application of methylprednisolone in severe and critical patients may improve outcomes and lung function without negative impacts on specific SARS-CoV-2 IgG production. |
| 25| Lu Chen   | 51  | Retrospective Observational | Methylprednisolone, Hydrocortisone or Dexamethasone ≥ 1 mg/kg ED | 244         | x       | Hospitalized patients                               | x       | Limited effect of corticosteroid therapy could pose to overall survival of critically ill patients with COVID-19. Given the adverse effects, corticosteroid therapy must be commenced with caution, and prudent dosage should be promoted under certain circumstances. |
| 26| Ma Qi     | 52  | Retrospective Observational | Methylprednisolone 2 study- groups: High: ≥ 1 mg/kg ED Low: < 1mg/kg ED | 72          | x x x   | Severe and critical patients                        | x x x   | Corticosteroids cannot reduce the hospital mortality, and is not associated with delayed viral clearance, but it could relieve the inflammatory storm and improve clinical symptoms in brief. Patients with severe COVID- |
19 could benefit from low-dose corticosteroids.

| 27 | Ma Zeng | 53 | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED | 450 | Severe and non-severe patients | x | x | x | x | x | 4 | Corticosteroids use may be accompanied by increased use of antibiotics, longer hospitalization, and prolonged viral shedding. |
| 28 | Majmundar | 54 | Retrospective Observational | Prednisolone, Dexamethasone, Methylprednisolone ≥ 1 mg/kg ED | 205 | Hospitalized patients | x | x | x | x | x | 6 | Corticosteroids were associated with a significantly lower risk of the ICU transfer, intubation, or in-hospital death. |
| 29 | Mikulská | 55 | Retrospective Observational | Methylprednisolone high and low ED | 215 | Hospitalized non-intubated patients | x | x | x | x | x | 6 | Early adjunctive treatment with tocilizumab, methylprednisolone or both may improve outcomes in non-intubated patients. |
| 30 | Nelson | 56 | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED | 117 | ICU patients on Mechanical Ventilation | x | x | x | x | x | 8 | Methylprednisolone was associated with increased ventilator-free days and higher probability of extubation in a propensity-score matched cohort. |
| 31 | Rodríguez | 57 | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED | 1014 | Hospitalized patients | x | x | x | x | x | 7 | Tocilizumab should be prioritized for being tested in randomized trials targeting patients with data suggestive of a hyperinflammatory state. The results for PDC were less consistent but are also encouraging. |
| 32 | Rubio | 68 | Retrospective Observational | Unknown | 92 | ICU and General ward patients | x | x | x | x | x | 5 | The early use of GC pulses could reduce the use tocilizumab and might decrease events such as intubation and death. |
| 33 | Salton | 58 | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED | 173 | ARDS patients | x | x | x | x | x | 8 | Per-protocol administration of prolonged low-dose methylprednisolone treatment is associated with a significantly lower hazard of death, reduced ICU burden and decreased ventilator dependence. |
| 34 | Shen Zheng | 59 | Retrospective Observational | Methylprednisolone unknown dose | 325 | Hospitalized patients | x | x | x | x | x | 4 | COVID-19 cases in Shanghai were imported. Rapid identification, and effective control measures helped to
contain the outbreak and prevent community transmission.

| No. | Last Name | First Name | Study Type | Intervention | Patient Characteristics | n | Outcomes | Risk of Bias |
|-----|-----------|------------|------------|--------------|-------------------------|---|----------|--------------|
| 35  | Shi Wu    | 71         | Retrospective Observational | Unknown | Hospitalized patients | 99 | x | 4 | SARS-CoV-2 RNA clearance time was associated with sex, disease severity, and lymphocyte function. The current antiviral protocol and low-to-moderate dosage of corticosteroid had little effect on the duration of viral excretion. |
| 36  | Tomazini  | 37         | Randomized controlled trial | Dexamethasone ≥ 1 mg/kg ED | ICU patients with moderate to severe ARDS | 299 | x | x | Risk of Bias | Dexamethasone plus standard care compared with standard care alone resulted in a significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days. |
| 37  | Wang Jiang| 60         | Retrospective Observational | Methylprednisolone ≥ 1 mg/kg ED | Severe hospitalized patients | 46 | x | x | 7 | Early, low-dose and short-term application of methylprednisolone was associated with better clinical outcomes in severe CoVID-19 patients, and should be considered before onset of ARDS. |
| 38  | Wang Yang | 67         | Retrospective Observational | Unknown | Hospitalized patients | 69 | x | 4 | COVID-19 shows frequently fever, dry cough, and increase of inflammatory cytokines, and induced a mortality rate of 7.5%. Older patients or those with comorbidities are at higher risk of death. |
| 38  | Wang Zhang| 69         | Retrospective Observational | Unknown | Not Reported | 548 | x | 6 | Low-dose or no glucocorticoid treatment was associated with a lower hazard compared with high-dose treatment (≥ 1 mg/kg) for 15-day in hospital death. |
| 40  | Wu Chen   | 61         | Retrospective Observational | Methylprednisolone unknown dose | Hospitalized patients | 201 | x | 4 | Treatment with methylprednisolone may be beneficial for patients who develop ARDS. |
| 41  | Wu Huang  | 62         | Retrospective Observational | Methylprednisolone < 1 mg/kg ED | Severe or Critical patients | 1763 | x | 7 | Corticosteroid use was not associated with beneficial effect in reducing in-hospital mortality for severe |
Prolonged SARS-CoV-2 RNA shedding was associated with male sex (P = .009), old age (P = .033), concomitant hypertension (P = .009), delayed admission to hospital after illness onset (P = .001), severe illness at admission (P = .049), invasive mechanical ventilation (P = .006), and corticosteroid treatment (P = .025).

Possible short-term clinical improvements with corticosteroid. Emphasis the urgent need for high-quality studies on Steroids and outcome in critically ill COVID-19 patients.

No evidence of clinical benefit of corticosteroids was found for those without acute respiratory distress syndrome. Virus clearance may be slower in people with chronic HBV infections.

Table 2. Summary of Findings

| No | Author | Study Design | Intervention | Comparator | Study Population | Outcomes | R.O.B. | Notes |
|---|---|---|---|---|---|---|---|---|
| 42 | Xu Chen | Retrospective Observational | Methylprednisolone < 1 mg/kg ED | 113 Hospitalized patients | x x | 5 | or critical cases in Wuhan. |
| 43 | Yang Lipes | Retrospective Observational | Methylprednisolone, Hydrocortisone or Dexamethasone ≥ 1 mg/kg ED | 15 ICU patients | x x | 6 | Possible short-term clinical improvements with corticosteroid. Emphasis the urgent need for high-quality studies on Steroids and outcome in critically ill COVID-19 patients. |
| 44 | Zha Li | Retrospective Observational | Methylprednisolone < 1 mg/kg ED | 31 Hospitalized patients | x x x | 5 | No evidence of clinical benefit of corticosteroids was found for those without acute respiratory distress syndrome. Virus clearance may be slower in people with chronic HBV infections. |

α M = mortality; V = Viral Clearnance; H = Length of hospital stay; R = Mechanical Ventilator/respirator; O = Oxygenation; I = Secondary infections.
β Randomized Embedded Multifactorial Adaptive Platform trial
γ ED = Prednisolone Equivalent Dose
δ Newcastle Ottawa Scale (N.O.S.) for Retrospective observational studies. Risk of Bias (R.O.B.) for Randomized controlled trials: see figure 2.

**Table 2. Summary of Findings**

**Effect of Corticosteroids in hospitalized CoVID-19 patients.**

*Intervention: Corticosteroids; Comparison: Standard of Care*
| Outcomes                        | total n° events/total n° of patients | Relative effect (95% CI) | N° of participants (studies) | Certainty of evidence (Grade α) | Comments                                                                 |
|--------------------------------|--------------------------------------|--------------------------|-----------------------------|--------------------------------|-------------------------------------------------------------------------|
| In-hospital Mortality          | standard care: 1547/9080 (17.0%)      | corticosteroids: 1173/5234 (22.4%) | Estimate 0.72 (0.57 - 0.87)  | 14.187 (22)                  | Corticosteroids reduce mortality in CoVID-19 hospitalized patients     |
| Requirement of Mechanical ventilation | 124/467 (26.6%)                        | 89/472 (18.9%)           | Estimate 0.70 (0.54 - 0.91)  | 939 (7)                       | 17 studies reported on mechanical ventilation, but effects could only be quantified in 7 studies. |

**Descriptive results:**

- **Viral Clearance:** In corticosteroid group viral clearance time ranged from 10 to 29 days in corticosteroids group and from 8 to 24 days in standard of care group.
- **Length of hospital stay:** Conflicting results both in favor and against the use of corticosteroids.
- **Mechanical Ventilation:** In 14 out of 17 studies, corticosteroids therapy is associated with beneficial effects on ventilator free days, on respiratory failure requiring mechanical ventilation and time on mechanical ventilator.
- **Oxygenation:** Outcome reporting in Saturation, p/F ratio and Oxygen demand. Conflicting results in favor and against the use of corticosteroids.
- **Secondary infections:** In five out of six studies, secondary infections and antibiotic use are increased.

α Details on GRADE score are available in Appendix 10.

β Due to mortality analyses in subsets of patients, this number of participants is lower than the sum of sample sizes from the included study.

**Figures**
Figure 1
Flowchart article selection.docx
### Figure 2

**Forest plot Mortality.docx**

| Author (reference) | RR (95% CI) | Sample size[^3] | Weight[^3] | Quality assessment |
|--------------------|-------------|-----------------|------------|--------------------|
| Dequin, et al.[29] | 0.67 [0.38, 1.17] | 32 | 18.4% | A B C D E F G H I (ROB) |
| Fadel, et al.[30] | 0.61 [0.38, 0.98] | 213 | 25.2% | A B C D E F G H I (NOS) |
| Jeronimo, et al.[31] | 1.15 [0.62, 2.11] | 188 | 16.1% | A B C D E F G H I (ROB) |
| Ma, Zheng, Zhan, et al.[32] | 2.90 [0.39, 21.53] | 82 | 1.7% | A B C D E F G H I (NOS) |
| Majnudar, et al.[33] | 0.74 [0.40, 1.35] | 205 | 16.4% | A B C D E F G H I (NOS) |
| Salton, et al.[34] | 0.58 [0.33, 1.04] | 173 | 17.8% | A B C D E F G H I (NOS) |
| Wang, Jiang, He, et al.[35] | 0.33 [0.10, 1.12] | 46 | 4.4% | A B C D E F G H I (NOS) |
| **Overall** (I-squared = 10.8%, p = 0.347) | 0.70 [0.54, 0.91] | 939 | 100.0% | A B C D E F G H I |

[^3]: Weights are from random-effects analyses
[^4]: Due to mortality analyses in subsets of patients, the number of participants can be lower than the actual included patients per study.
Figure 3

Forest plot Mechanical ventilation.docx

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.Searchstrategy.docx
- Appendix2.Dataextractionform.docx
- Appendix3.Excludedreferences.docx
- Appendix4.DataextractionGeneralinformation.docx
- Appendix5.NOSscore.xlsx
- Appendix6.Dataextractiontreatment.docx
- Appendix7.DataextractionOutcomes.docx
- Appendix8.ViralClearancetime.docx
- Appendix9.MechanicalVentilation.docx
- Appendix10.GRADECLASSIFICATION.docx
- Appendix11.Populationbias.docx