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Corticosteroids use for COVID-19: an overview of systematic reviews

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SUMMARY

Purpose: A reappraisal of the validity of the conclusions of systematic reviews (SRs) and meta-analyses related to corticosteroids use for the treatment of COVID-19.
Material and Methods: An overview of SRs (umbrella review). The methodological quality of the SRs was assessed using tha AMSTAR-2 checklist; quality of the evidence was appraised following the GRADE approach.
Results: 35 SRs were included in this overview. Data were from 307 overlapping reports, based on 121 individual primary studies (25 randomized clinical trials (RCTs), 96 non-RCTs. In critically ill patients the use of steroids significantly reduced mortality compared to standard of care in 80% of the SRs, more often with moderate/high level of certainty; however, in patients not requiring oxygen supplementation the use of steroids increased the overall mortality in 2/3 of the comparisons. Clinical progression of diseases (need for mechanical ventilation, or for intensive care admission) was more commonly observed among controls compared to steroids recipients (in 9 out of 14 comparisons; certainty of evidence from very-low to moderate). The occurrence of adverse events was similar among steroids recipients and controls. Other outcomes (*i.e.*, viral clearance, length of hospital stay) or issue related to optimal dose and type of steroids were addressed in a minority of SRs, with a high level of uncertainty, so that no definitive conclusions can be drawn.
Conclusions: There is moderate certainty of evidence that corticosteroids reduce mortality and progression of disease in critically ill COVID-19 patients compared to standard of care, without increasing the occurrence of adverse events.

Keywords: Systematic review, meta-analysis, umbrella review, COVID-19, corticosteroids.

INTRODUCTION

The available evidence indicates that the rapid clinical progression of the diseases in patients with COVID-19 is directly related to the hyperinflammatory syndrome caused by a dysregulated host innate immune response [1]. Acute respiratory distress syndrome (ARDS) is one of the primary causes of death in patients with COVID-19 and is largely caused by elevated levels of pro-inflammatory cytokines (IL-6, IL-1, TNF-α, and interferon) referred to as cytokine storm [1, 2]. Not surprisingly, this has stimulated the development of anti-inflammatory therapies for the treatment of patients with COVID-19, and among them the use of IL- inhibitors and corticosteroids has been the object of numerous clinical studies, with inconsistent results [3-8]. Corticosteroids are used in several pulmonary disorders, including Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). While at the beginning of the SARS-CoV-2 pandemic the World Health Organization (WHO) counselled against use of corticosteroids in COVID-19 patients, after the publication of RECOVERY trial the WHO changed its initial advice and recommended the use of corticosteroids in patients with severe COVID-19 [4, 5, 9]. Given that, a considerable number of clinical trials have been conducted with the aim of evaluating the efficacy and safety of corticosteroids for COVID-19 patients, and oth-

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ers are in progress or in development. Due to the large amount of clinical data available, a number of systematic reviews (SRs) and meta-analysis have been published in the latest years. Nevertheless, their conclusions are quite inconsistent and reveal the extensive heterogeneity among studies in terms of design, conduct, and reporting. The current study is an overview of systematic reviews, also called umbrella review, and is aimed to reappraise the validity of the conclusions of the SRs and meta-analyses related to corticosteroids use for the treatment of COVID-19.

MATERIALS AND METHODS

This umbrella review is a part of a protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021259625.

Review question/objective
The aim of this umbrella review is to evaluate the efficacy and safety of corticosteroids for the treatment of COVID-19 patients.

Inclusion and exclusion criteria
We considered for inclusion in this overview SRs that comprised randomized controlled trials (RCTs) and non-RCTs (*i.e.*, prospective, retrospective, cross-sectional, cohort studies and case series) assessing the safety and efficacy of corticosteroids for the treatment of COVID-19 patients. Traditional reviews with no clear methodological approach were excluded from this umbrella review. SRs evaluating other viral infections were excluded unless they also reported data on SARS-CoV-2 infection that could be evaluated separately.

Clinical setting and participants
For this umbrella review, we considered SRs on COVID-19 at any stage of disease severity, from asymptomatic/pauci-symptomatic to life-threatening cases, and in any setting (outpatients and hospitalized patients).

Intervention and outcomes
Treatment with corticosteroids at any dose, timing and frequency was compared to standard of care (SOC) or placebo. We included the following outcomes: overall mortality, viral clearance, clinical progression, length of hospital stay, adverse reactions. Where available, we reported also results of subgroup analyses based on the severity of COVID-19 and on the design of the studies included in the SRs.

Search strategy
Relevant studies in four bibliographic databases (Embase, PubMed, Web of Science, and Cochrane library) were searched up to July 2022. The searches were carried-out without languages restriction using Medical Subjects Heading: ("COVID-19" OR "SARS-CoV-2") AND ("systematic review" OR "meta-analysis"). Furthermore, we checked the reference lists of the most relevant manuscripts (original studies and reviews) to identify potentially eligible studies not captured by the electronic literature search.

Study selection and data extraction
All titles were screened by two independent assessors (MC and IP). Eligibility assessment was based on the title or abstract and on the full text if required. Full texts of possibly eligible articles were obtained and assessed independently by two reviewers (MC and IP). Both reviewers compared the articles identified. The two assessors also independently extracted quantitative and qualitative data from each selected study, with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (FM). Findings are presented in tabular format with supporting text (Table 1). Quantitative tabulation of results includes: first author name and year of publication, the clinical condition under evaluation, principal characteristics of the study population, number of RCTs and non-RCTs included in the SR, intervention and control group, the outcomes assessed, and the main conclusion of the review as reported by authors.

Assessment of methodological quality of systematic reviews
We used the AMSTAR-2 critical appraisal checklist for SRs, a tool that evaluates both quantitative and qualitative reviews [10]. The tool is suitable for reviews including randomised and non-randomised studies. It includes 16 domains (7 considered critical) relating to the research question, review design, search strategy, study selection, data extraction, justification for excluded stud-

ies, description of included studies, risk of bias, sources of funding, meta-analysis, heterogeneity, publication bias, and conflicts of interest (see Table 2 for details of each question). Two review authors (MC, IP) independently assessed the quality of evidence in the included reviews and the methodological quality of the SRs. We resolved discrepancies through discussion or, if needed, through a third review author (FM). We did not exclude reviews based on AMSTAR 2 ratings, but considered the ratings in interpretation of our results.

Summary of the evidence and appraisal of the quality of evidence

For the quantitative synthesis, we reported the effect size (odds ratio [OR], risk ratio [RR], risk difference [RD], Hazard ratio [HR] or risk difference [RD] with the 95% confidence intervals [CI]), as reported in individual reviews, and the main conclusions of each systematic review/meta-analysis The quality of evidence was appraised following the GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation). Whenever available, the grading of

Table 1 - Methodological quality of Systematic reviews assessed with the AMSTAR-2 tool.

Author, year [reference]	*AMSTAR-2 DOMAIN*															
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
Yousefifard, 2020 [12]																
Lee, 2020 [13]																
Li, 2020 [14]																
Yang, 2020 [15]																
Cantini, 2020 [16]																
Cheng, 2020 [17]																
Wang, 2020 [18]																
Sarma, 2020 [19]																
Tlayjeh, 2020 [20]																
WHO REACT Working Group, 2020 [21]																
Ye, 2020 [22]																
Van Paassen, 2020 [23]																
Chaudhuri, 2021 [24]																
Hasan, 2021 [25]																
Ma, 2021 [26]																
Pasin, 2021 [27]																
Pulakurthi, 2021 [28]																
Sahu, 2021 [29]																
Tu, 2021 [30]																
Cano, 2021 [31]																
Moosazadeh, 2021 [32]																
Nguyen, 2021 [33]																
Ferreto, 2021 [34]																
Yu, 2021 [35]																
Sahilu, 2021 [36]																
Boppana, 2021 [37]																
Wagner, 2021 [38]																

Continue >>>

Continue >>>

Author, year [reference]	*AMSTAR-2 DOMAIN*															
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
Tan, 2022 [39]																
Chaharom, 2022 [40]																
Caiazzo, 2022 [41]																
Mohanty, 2022 [42]																
Griesel, 2022 [43]																
Hong, 2022 [44]																
Thakur, 2022 [45]																
Khokher, 2022 [46]																

	Methodological requirement met
	Methodological requirement partly met, or not specified
	Methodological requirement unmet

Foot-note Amstar-2 domains consists of the following 16 items:

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Critical domains include items 2, 4, 7, 9, 11, 13, and 15. [10].

Table 2 - Mortality data: comparisons based on the design of Systematic Reviews (SRs).

	SRs based on RCTs only	*SRs based on RCTs and non-RCTs*	*SRs based on non-RCTs only*
No. SRs (no. comparisons)	14 (22)	17 (20)	5 (6)
Quality of the evidence: no (%)	High: 1 (4.5) Moderate: 9 (40.9) Low: 11 (50) Very-low: 1 (4.5)	High: – Moderate: 6 (30) Low: 8 (40) Very-low: 6 (30)	High: – Moderate: – Low: – Very-low: 6 (100)
Effect size of steroids: no (%)	Reduction of mortality: 13 (59) Unclear results: 8 (36.3) Increased mortality: 1 (4.5)	Reduction of mortality: 10 (50) Unclear results: 8 (40) Increased mortality: 2 (10)	Reduction of mortality: 2 (33.3) Unclear results: 3 (50) Increased mortality: 1 (16.6)

Footnote: SR, systematic review; RCT, randomized clinical trial. For the outcome mortality, a total of 48 comparisons were available from the 36 SRs included in the umbrella review.

the quality of evidence reported in the included reviews was considered to define the quality of evidence. When grading of evidence was not reported by the authors of the study, the GRADE approach was applied in its five domains (risk of bias, indirectness, imprecision, inconsistency, and publication bias) basing on the information available from the study [11].
Furthermore, a three-color score was used for an immediate visual inspection of the comparison between intervention (steroids) and controls with regards to the main outcomes assessed: overall mortality, viral clearance, clinical progression, length of hospital stay, adverse events (green color: steroids confer advantage over standard therapy or placebo; red color: steroids do not confer advantage over standard therapy or placebo; yellow color: no clear advantage or disadvantage).

RESULTS

The electronic and manual search retrieved 4202 references The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is reported in Figure 1. At the first stage of screening titles and abstracts, 45 references were selected. After the full texts were examined with regards to inclusion and exclusion criteria, 35 SRs were included in the umbrella review [12-46]. Ten SRs were excluded [47-56]. Reasons for exclusion were: SRs not covering or with no informative data on steroids therapy in COVID-19, protocol of a SR, case series [47-56].

Description of the studies
Of the 35 SRs included in the overview, 29 were focused exclusively on COVID-19, while 6 focused also on other critical coronavirus infections (*e.g.*, severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS) [12-15, 22, 40]. The 35 SRs included 307 overlapping reports (98 RCTs and 209 non-RCTs), based on 121 individual primary studies. The primary studies included 25 RCTs, 84 controlled non-RCTs, and 12 uncontrolled studies (single arm studies, including case series and case reports). Thirty-four SRs focused on systemic steroids as treatment of COVID-19, while one review [43] was focused on inhaled use of steroids. The main characteristics of the SRs included are summarized in Supplementary Table 1.

Methodological quality (Table 2)
Of the included reviews, two Cochrane reviews met all the AMSTAR-2 methodological requirements, and 4 (11.4%) had more than one unmet methodological requirements [15, 16, 18, 33, 38, 43]. Thirty-three reviews (94.2%) had 1 or more (from 1 to 8) methodological requirements partly met. Only 3 reviews (12.5%) report on the source of funding for the studies included in the review; 5 reviews (14.2%) did not mention that the methods of the review were registered in a protocol. Twelve reviews (34.2%) did not mention publication bias in material and methods and results,

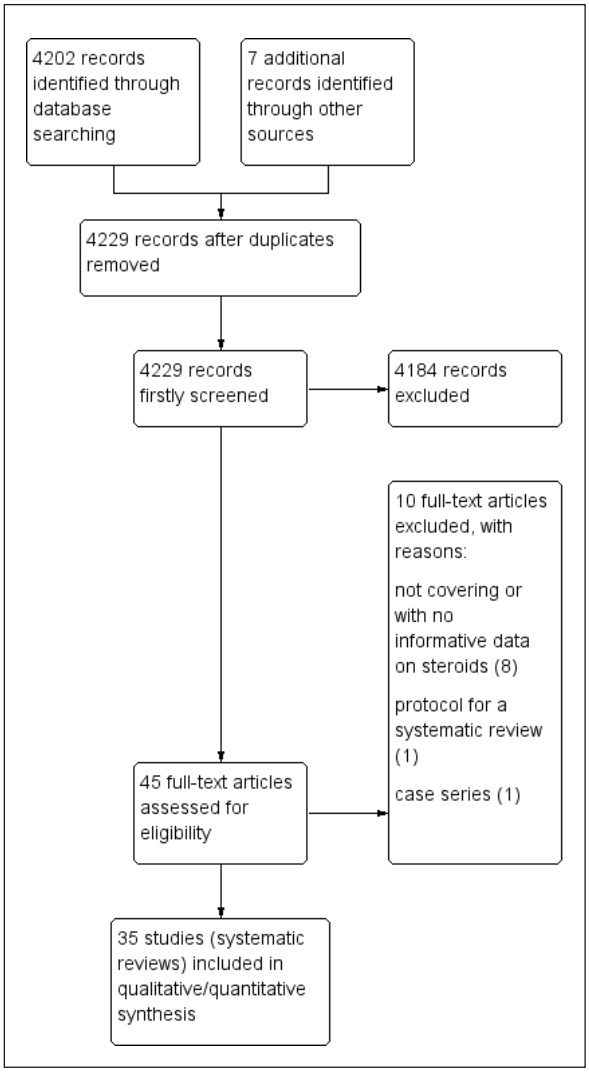

Figure 1 - Flow chart of study selection process.

and failed to discuss the possible impact of publication bias on review findings. In one review participants, interventions, comparators, and outcomes (PICO) were not clearly made explicit, but in the remaining 34 reviews the design of the study was fully explained. In 8 reviews the search strategy was not comprehensive, mostly because the search did not include EMBASE. Study selection and screening was performed in duplicate by 88.5% of authors team (31/35). Other unmet or partly-met domains were related to the list of excluded reviews and reasons (1 and 5 reviews, respectively), assessment of risk of bias (4 and 4 reviews, respectively), and assessment of the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis (4 and 2, respectively).

Summary of the effect of steroids on the main outcomes

Outcome "overall mortality"

Overall mortality was the most common reported outcome. Great heterogeneity was observed in several SRs; hence, when possible, we performed subgroup analyses to control for sources of heterogeneity such as severity of clinical conditions (*e.g.*, according to the requirement of O_2 supplementation, ICU admission, need of mechanical ventilation), design of studies included in the review (*e.g.*, RCTs and non-RCTs), corticosteroids regimen used. The results of our analyses are summarized in Supplementary Table 2. Thirty-one SRs reported the outcome mortality, 14 including data only from RCTs [16, 21, 24-28, 30, 33, 34, 37, 41, 38], 5 from non-RCTs only 15, 17, 18, 22, 32], and the remaining 12 from both RCTs and non-RCTs [12-14, 19, 20, 23, 29, 31, 35, 36, 39, 40, 42-46]. A total of 48 comparison between steroids recipients and controls were performed in the included SRs, as summarized in supplemenrary Table 1 and supplementary table 2. The quality of the evidence according to the GRADE assessment was very-low in 13 comparisons, low in 19, moderate in 15, and high in one comparison. In 25 (52%) of these comparisons the effect size favoured the steroids arm compared to controls (level of evidence: high/moderate in 14 comparisons, low/very-low in 11), in five (10.4%) favoured the control arm (low or very-low level of evidence), while in 18 comparisons (37.5%) it was unclear if steroids reduced mortality compared to controls (level of evidence moderate in 2 comparisons, low or very-low in 16). As expected, the quality of the evidence was on average higher in SRs of RCTs only (Table 2). Moreover, compared to SRs including RCTs+non-RCTs and non-RCTs, SRs including RCTs only reported more commonly a reduction of mortality in steroids recipients than in controls (Table 2).

We also performed subgroup analysis of mortality according to severity of COVID-19, although this was limited by the heterogeneity in defining the clinical condition and inconsistency in reporting stratified data. In critically ill patients, including those requiring invasive mechanical ventilation and those with ARDS, the use of steroids therapy was found significantly more effective in reducing mortality compared to controls not receiving steroids in 80% (12/15) of the comparisons (low/very-low certainty of evidence in 5 comparisons, moderate/high in 7) [16, 19-24, 27, 31, 34, 37, 41], of unclear efficacy in 13% (2/15) of the comparisons (low and very-low certainty) [30, 36], and less effective than control in 1 comparison (very-low- certainty of evidence) [22]. By contrast, when the comparison included patients with different severity of infection (from severe to critical), the results were more heterogeneous, and the effect size favoured steroids use only in 12 out of 23 comparisons (52%); unclear results were reported in 10 comparisons (43%), and increased mortality in 1 comparison. However, in patients not requiring O_2 supplementation the role of steroids compared to controls was detrimental in 4 out of 6 comparisons (66.6%; low certainty of evidence) [27, 29, 30, 41], and unclear in 2 comparisons [16, 37] (moderate and very-low certainty of evidence).

One SR [43] evaluated the use of inhaled steroids in asymptomatic SARS-CoV-2 infection or mild COVID-19, and concluded that it is unclear whether inhaled steroids + SOC reduces mortality compared to SOC alone (RR 0.61, 95% CIs 0.22/1.67; low level of certainty).

Outcome "Adverse events"

Adverse events were often not reported in the systematic reviews and, when reported, there was often inconsistency in describing type and severity of adverse events. In some of the systematic reviews there were just general statements about a similar occurrence of adverse events across groups of intervention. An effect size for serious adverse events and/or for any adverse events related to

steroids was reported in 9 SRs for a total of 16 comparisons [15, 20, 21, 24, 26, 28, 30, 43, 44]; data were from 39 reports, based on 24 individual primary studies (11 RCTs and 13 non-RCTs). In 13 out of 16 comparisons (81%) the occurrence of adverse events (serious adverse events, any adverse events, gastrointestinal bleeding, secondary infections and hyperglycemia) were similar between steroids recipients and controls (Supplementary Table 2); the occurrence of adverse reactions was significantly higher in steroids recipients compared to control groups in 2 comparisons evaluating the occurrence of bacterial infection (very-low quality of certainty), and one evaluating the occurrence of hyperglycemia (moderate quality of evidence).

Outcome "clinical progression of disease"

Clinical progression of diseases was reported in 12 SRs (Supplementary Table 2), more commonly as need for mechanical ventilation (10 comparisons), or as need for ICU admission (2 comparisons), or as a clinical progression composite score (2 comparisons). Data were from 66 reports, based on 24 individual primary studies (7 RCTs and 17 non-RCTs). In 9 out of 14 comparisons (64.2%) the effect size favoured steroids compared to controls (from very-low to moderate certainty of evidence), in 3 it was unclear whether steroids decreased rate of clinical progression compared to controls (low certainty of evidence), while in one comparison based on 2 non-RCTs steroids increased rate of clinical progression compared to controls (very-low certainty of evidence).

Outcome "length of hospital stay"

Length of hospital stay was reported in 4 SRs, basing on 23 reports [17, 24, 29, 40]. Three SRs concluded that it is unclear if steroids decrease length of hospital stay compared to controls, while one shows a reduction of LOS in steroids recipients (Supplementary Table 2). The quality of evidence was graded as low.

Outcome viral clearance

The outcome viral clearance (rate of patients with negative reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 after a positive test at baseline) was reported in 5 SRs [17, 19, 20, 29, 44], basing on 29 reports (22 primary studies, including 1 RCT). In 3 SRs the viral clearance was not delayed in steroids recipients compared to controls (very-low certainty of evidence), but in 2 SRs [20, 29] the viral clearance in steroids recipients was delayed compared to controls (very-low certainty of evidence).

Steroids regimens

Data on the effect of pulse dose, high dose and/or low dose steroids were available from 5 SRs for the outcome mortality, from 4 SRs for the outcome progression of disease, from 2 SRs for the outcome length of hospital stay, and from one SR for the outcome adverse events (Supplemantary Table 2).

For the outcome mortality, low-dose steroids were found as effective as high-dose steroids in 2 comparisons from a SR (certainty of evidence from low to very-low) [39]. Low-dose steroids were found more effective than SOC in 2 SRs (certainty of evidence low and moderate) [30, 44], and as effective as SOC in one SR (VL certainty of evidence) [31]. High-dose steroids were found as effective as SOC in 2 SRs (low certainty of evidence) [31, 44].

For the outcome progression of disease (need for mechanical ventilation in 4 SRs, and admission to ICU in one), low-dose steroids were found as effective as high-dose steroids in 2 SRs [39, 42], and more effective than SOC in one SR [44] (from very-low to low certainty of evidence). High-dose steroids were found as effective as SOC in one SR (low certainty of evidence) [44].

Length of hospital stay was similar among patients receiving non-pulse dose or pulse-dose steroids [46], and in patients receiving high-dose or low-dose steroids (from low to very-low certainty of evidence) [39]. Likewise, no clear difference in the occurrence of hyperglicemia and secondary infections were found among low-dose and high-dose steroids recipients (moderate certainty of evidence) [39].

DISCUSSION

Umbrella reviews assemble together several systematic reviews on the same condition, and permit to consider for inclusion the highest level of evidence available, such as systematic reviews and meta-analyses [57, 58]. In this umbrella review we have reappraised the results of 35 SRs, published between 2020 and 2022, on the clinical use of steroids for COVID-19. The SRs included

in this overview present data from 307 overlapping reports (98 RCTs and 209 non-RCTs), based on 121 individual primary studies (25 RCTs, 84 controlled non-RCTs, and 12 uncontrolled studies). We believe that makes this the largest review to date within this subject area, and hope this will make it particularly helpful to decision makers.

The main findings of this umbrella review are the following:

1) In critically ill patients (*e.g.*, those requiring invasive mechanical ventilation and those with ARDS) the use of corticosteroids therapy was found significantly more effective in reducing mortality compared to SOC; this was demonstrated in 80% of the SRs (12/15) reporting this outcome, more often with moderate/high level of certainty (7/12).
2) When patients with different severity of infection were compared (from severe to critical), the results were more heterogeneous, and a decrease in mortality was reported in only 52% of the SRs.
3) In patients not requiring oxygen supplementation the use of steroids compared to controls increased the overall mortality in 4 out of 6 comparisons (66.6%).
4) Rate of clinical progression of diseases (more commonly defined as need for mechanical ventilation) was significantly higher in patients receiving SOC compared to steroids recipients, as demonstrated in 64.2% of the SRs reporting this outcome; the available evidence was graded from very-low to moderate.
5) In more than 80% of the SRs the occurrence of adverse events (serious adverse events, any adverse events, gastrointestinal bleeding, secondary infections and hyperglycemia) was similar among steroids recipients and controls; however, findings on the occurrence of adverse events can be biased because adverse events were often not reported in the systematic reviews and, when reported, there was often inconsistency in describing type and severity of adverse events.

Earliest published SRs/meta-analyses often included patients from observational studies, and also included data of coronavirus diseases caused by SARS-CoV-2, severe acute respiratory syndrome coronavirus, and Middle Eastern respiratory syndrome. Limitations to the methodological quality of reviews most commonly related to absence of publication bias assessment and funding sources of primary studies. Other limitations were rarely found, and usually were more commonly recorded in earliest published SRs, probably in relation to methodologic limitations of the primary studies available in that moment.

The clinical picture of COVID-19 has changed over time, both due to the emergence of viral variants and the spread of vaccinations. This obviously leads to additional difficulty in trial design and data analysis and interpretation. Overall, patients receiving corticosteroids with coronavirus diseases in the early phase of the epidemic were more likely to be critically ill; hence, there was a significant selection bias in non-RCTs included in the SRs. In this extremely uncertain and changing context, typical of emergency situations such as those of the COVID-19 pandemic, it is evident that also systematic reviews and meta-analyses have produced heterogeneous results [59, 60]. The results of RCTs are not always consistent with the results of observational studies, and differences in estimated magnitude of treatment effect are very common, often resulting in overestimation of treatment effects in observational studies [61]. Interpretation of the results obtained from both RCTs and observational studies, as well as from systematic reviews including both types of study design, can help understand the efficacy/effectiveness and safety of a therapeutic options [62]. For this reason, we performed, where possible, subgroup analyses of the effect size obtained in the overall comparison, in RCTs and in observational studies. For the outcome most commonly reported, overall mortality, it was possible to perform subgroup analysis of SRs according to study design and severity of COVID-19 at baseline. It was also clear that most of the included studies (both RCTs and non-RCTs) were at risk of bias and showed important clinical, methodological and statistical heterogeneity. Other outcomes (*i.e.*, viral clearance, and length of hospital stay) were addressed by only a minority of SRs with a high level of uncertainty, so that no definitive conclusions can be drawn. Likewise, some of the SRs addressed the issue of the optimal dose (*e.g.*, high and low-dose steroids) and type of steroids (*e.g.*, dexamethasone, methylprednisolone, hydrocortisone) to be used for the treatment of COVID-19. In this respect the data available from primary studies and SRs are heterogeneous and sparse, so

no firm conclusion can be drawn, but the interest in this area of research is timely and relevant, and several clinical trials evaluating the use of corticosteroids for the treatment of COVID-19 are underway or in development [63, 64].

Author contributions
Conceptualization: M.C and IP. Methodology: M.C. Data extraction: IP, FM, MC. Writing/preparation original draft: M.C. and IP. Writing/review and editing: IP, FM, SP, VDA. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest
The authors declare no conflict of interest in regard to this work.

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Supplemental Table 1 - Main characteristics of Systematic reviews included in the overview.

First author, year [ref]	*Clinical setting*	*Population*	*No. studies included in quantitative analysis*			*Intervention*		*Outcomes*	*Main results*
			Overall (patients)	*RCT*	*Non-RCT*	*Steroids*	*Control*		
Yousefifard, 2020 [12]	COVID-19, SARS-Co, and MERS-CoV	4498 pts., COVID-19 pts defined "severely ill"	15 (4498)	1	14	methylprednisolone, prednisolone, hydrocortisone and dexamethasone	Standard of care	Mortality, viral clearance, symptoms and lung function improvement, length of hospital stay	There is no evidence that corticosteroids are safe and effective on the treatment of severe COVID-19.
Lee, 2020 [13]	Patients with SARS, MERS and COVID-19	Steroids often in more severe cases	8 (4051). 3416 patients were diagnosed with SARS, 360 patients with MERS, and 275 (in 2 studies) with COVID-19	-	8	60.3% patients received steroids	No information provided	mortality	The meta-analysis including all studies showed no differences overall in terms of mortality In contrast, when the meta-analysis was performed restricting only to studies that used appropriate adjustment (e.g., time, disease severity), there was a significant difference between the two groups.
Li, 2020 [14]	Patients with SARS-CoV-2, SARS-CoV, or MERS-CoV infection:	Subjects were divided into those with severe-only and other (severe and not severe) cohorts	11 (5249). Studies were published 2003-2020 and were conducted in China and Saudi Arabia.	1	10 cohort studies	Methylprednisolone or hydricortisone	Standard of care	Efficacy endpoints studied included mortality, hospitalization duration, rates of ICU admission, use of mechanical ventilation, and a composite endpoint (death, ICU admission, or mechanical ventilation).	Corticosteroid use in subjects with SARS-CoV-2, SARS-CoV, and MERS-CoV infections delayed virus clearing and did not convincingly improve survival, reduce hospitalization duration or ICU admission rate and/or use of mechanical ventilation. There were several adverse effects
Yang, 2020 [15]	Patients with coronavirus infection; (from China and Saudi Arabia)	Critical and non-critical pts with SARS-CoV, MERS CoV, and SARS-CoV-2 infection	15 (5270) studies published from January 2002 to March 2020). 11 studies included pts. with SARS-CoV infection, 2 included pts with MERS-CoV infection, and the remaining 2 included pts with SARS-CoV-2 infection.	-	Retrospective analyses of case series or cohort of pts	Steroids (3176)	No steroids (1780)	the outcomes included the use of corticosteroids in critical and non-critical patients, mortality, length of stay and adverse reactions to corticosteroids.	Patients with severe conditions are more likely to require corticosteroids.
Cantini 2020 [16]	COVID-19 at any stage of disease severity	COVID-19 patients	Only 1 trial with steroids. Other treatment evaluated in this systematic review were antivirals, hydroxychloroquine, colchicine, and a variety of MAB	1 (6425)	-	Dexamethasone (2104 pts)	Standard of care (4321 pts)	Mortality	Dexamethasone reduced the mortality by one-third in ventilated patients
Cheng, 2020 [17]	patients with COVID- 19, mostly severe cases	Adult pts hospitalized for COVID-19	11 cohort studies, 2 retrospective cohort studies (without control group), and seven case reports (2840). One USA trial, the remaining from China	-	11 controlled trial	Corticosteroids	Standard therapy	The primary outcomes included clinical improvement, mortality, virus clearance time, and adverse events. The secondary outcomes included need of mechanical ventilation, length of ICU stay, hospitalization and hospital stay.	Corticosteroid did not significantly shorten the duration of symptoms but may promote clinical recovery; corticosteroid had no effect on mortality in patients with severe COVID-19; corticosteroid did not significantly reduce the virus clearance time, irrespective of severity; corticosteroid did not affect the need for mechanical ventilation, but significantly decreased length of ICU stay; corticosteroid therapy was associated with mild AEs
Wang, 2020 [18]	COVID-19 pts at any stage of disease severity	COVID-19 patients. Both severe and non.severe pts included, but more commonly non-severe pts	16 (3285) conducted in China	-	16 (case reports, case series, 2 retrospective cohorts)	Steroids	Usual care	Steroids use, mortality	Patients in critical conditions are more likely to receive corticosteroids. Moreover, there are no differences in mortality among COVID-19 pneumonia patients with or without corticosteroids treatment
Sarma, 2020 [19]	COVID-19 pts.	From mild to critical ilness	15 (5787 in pts with severe/critical ilness; 1566 with mild/moderate ilness)	3	12 cohort studies	most of the included studies used methylprednisolone dose up to 2 mg/kg/day	Standard of care, placebo	Mortality, requirement of ICU and mechanical ventilation	Among mechanically ventilated patients, steroid therapy may be beneficial in terms of reduced mortality. Among "severe and critical" patients; steroid therapy was associated with lowered mortality, decreased requirement of mechanical ventilation, and ICU. However, no benefit was observed in "mild to moderate" population
Tlayjeh, 2020 [20]	COVID-19 of different severities	Hospitalized pts	20 (16,977). Studies conduced in Europe, China and USA	1 (Recovery trial, 6425 pts)	19	Corticosteroids	Standard of care or placebo	10 studies examined the effect of steroids on short term mortality.. Four studies examined the effect of steroids on composite outcome of death, ICU admission and mechanical ventilation need. Six cohort studies examined the effect of steroids on viral clearance	Contrary to the results of the randomized trial in severe and critical COVID-19, the overall analysis shows that steroids use was not associated with reduction in short-term mortality but possibly with a delay in viral clearance in patients hospitalized with COVID-19 of different severities
WHO REACT Working Group, 2020 [21]	COVID-19 pts.	Critically ill patients	7 (1703) conducted in 12 countries (Australia, Brazil, Canada, China, Denmark, France, Ireland, the Netherlands, New Zealand, Spain, the UK, USA) from February to June 2020	7	-	Dexamethasone, hydrocortisone, or methylprednisolone (678 patients)	usual care or placebo (1025 patients)	The primary outcome measure was all-cause mortality at 28 days. A secondary outcome was investigator-defined serious adverse events.	Corticosteroids, use was associated with lower 28-day all-cause mortality. Adverse events varied across trials but there was no suggestion that the risk of serious adverse events was higher in patients assigned to corticosteroids except for the 2 smallest trials,
Ye, 2020 [22]	patients with COVID-19, severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), influenza, ARDS, CAP	Pts with different severity of infection (from ARDS to mild infections)	Data on COVID-19 pts very limited	7 RCT in ARDS pts, but no RCTs in COVID-19	Data on COVID-19 pts were limited to 2 observational studies in pts with severe infection and 1 cohort in ARDS COVID-19 pts	Steroids	Standard of care	Outcomes included mortality, length of intensive care unit stay, length of hospital stay, duration of mechanical ventilation, need for mechanical ventilation, viral clearance, adverse events	Corticosteroids may reduce mortality for patients with COVID-19 and ARDS. For patients with severe COVID-19 but without ARDS, evidence regarding benefit from different bodies of evidence is inconsistent and of very low quality.
Van Paassen, 2020 [23]	Covid-19	To study population varied from hospitalized patients (28/44) to patients admitted to the ICU (15/44)	44 studies, comprising 20.197 pts,	5	39	Different corticosteroid regimens, including methylprednisolone (28), prednisone (n=5) and dexamethasone (n=5) and hydrocortisone (n=4)	Standard of care	Primary outcomes were short-term mortality and viral clearance Secondary outcomes were: need for mechanical ventilation, need for other oxygen therapy, length of hospital stay and secondary infections	Frndings from both observational studies and RCTs confrm a beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation
Chaudhuri, 2021 [24]	adult patients with ARDS, including patients with COVID-19.	All patients included in the review were invasively ventilated	18 (2826). 8 trials were in COVID-19 pts, the remaining in pts with ARDS of different etiology	18	-	Steroids	Placebo or standard of care	Mortality, lenghy of hospital stay, adverse events	The use of corticosteroids probably reduces mortality in pts. with ARDS. This effect was consistent between patients with COVID-19 and non-COVID-19 ARDS, corticosteroid types, and dosage
Hasan, 2021 [25]	COVID-19	No information on severity of infections provided	5 RCT (652 pts)	5	-	Methlprednisolone, low and pulse dose	SOT	All-cause mortality	Low dose methylprednisolone did not reduce mortality compared to SOT, but pulse dose may reduce mortality
Ma, 2021 [26]	COVID-19	Severe COVID-19 patients	7 RCTs, 6250 patients	7	-	Hydrocortisone, methylprednisone, dexamethasone at various dosage and duration	SOT	All-cause mortality at the longest follow-up; a composite disease progression outcome, and incidence of serious adverse events	Corticosteroids were associated with a decreased all-cause mortality (27.3 vs. 31.1%), decreased the occurrence of composite disease progression (30.6 vs. 33.3%), and did not increase the incidence of serious adverse events (3.5 vs. 3.4%)
Pasin, 2021 [27]	COVID-19	Various severity of infections	5 RCTs, 7,692 pts	5	-	Hydrocortisone, methylprednisone, dexamethasone	SOT, placebo	Mortality rate, need of mechanical ventilation	Overall mortality of pts treated with steroids was lower than mortality of controls The same beneficial effect was found in the subgroup of pts. requiring mechanical ventilation., Steroids increased mortality in the subgroup of pts. not requiring oxygen.. Pts. treated with steroids had a lower risk of need for mechanical ventilation.
Pulakurthi, 2021 [28]	COVID-19	Pts with severe infections	8 RCTs, 7737 pts. (2795 /4942)	8	-	Corticosteroids plus standard of care (SOC)	placebo and/or SOC alone	Mortality, need for mechanical ventilation, serious adverse events	Mortality and need for mechanical ventilation were significantly lower in steroids recipients.. There was no significant difference between the corticosteroid and SOC groups with regards to Serious AEs and superinfections.
Sahu, 2021 [29]	COVID-19	non-oxygen requiring pts	7 trials, 2214 pts	4	3	Methylprednisolone (dose ranging from 20 mg/day to 2 mg/kg/day) was used in all the studies except in the RECOVERY trial where dexamethasone (6 mg/day) was used.	SOT	Progressing to severe disease, mortality, duration of fever, duration of viral clearance and length of hospital stay	Steroids in non-oxygen requiring COVID-19 patients can be more detrimental than beneficial.
Tu, 2021 [30]	COVID-19	Hospitalized pts.	10 RCTs, 12473 pts	10	-	Methylprednisolone, dexamethasone, hydrocortisone	Standard treatment or placebo	Mortality, adverse events; need for invasive mechanical ventilation (for patients not intubated at inclusion) and secondary infections	Corticosteroid treatment did not convincingly improve survival in severe COVID-19 patients. But the low dose dexamethasone appear to have a role in the management of severe COVID-19 patients
Cano, 2021 [31]	COVID-19 pts	Pts, with different severity of infections. Steroid use was reported widely in mechanically ventilated patients (35.3%), ICU patients (51.3%), and severe COVID-19 patients (40%)	73 studies, 21350 covid-19 pts (4618 receiving steroids). 33 studies (13654 pts) were included in the quantitative analysis	1	72 comparative, non RCTs (4 with propensity score matching	The use of corticosteroids (mostly methylprednisolone, dexamethasone, or hydrocortisone) across studies was highly variable	SOT	Mortality, ICU admission, mechanical ventilation, and viral shedding	Corticosteroids showed mortality benefit in severelly ill COVID-19 patients. further high-quality clinical trials to define the most beneficial timing and dosing for corticosteroids are needed.
Mousazadeh, 2021 [32]	COVID-19 pts	No further information on COVID-19 pts provided	5 cohort studies (1431)	-	5	Combination therapy with tocilizumab and steroids (568 pts)	Tocilizumab alone (303 pts) or standard of care (without steroids and/ or tocilizumab; 560 pts)	Mortality	Mortality was significantly lower in steroids + tocilizumab group compared to the standard of care group, but was similar in the comparison between steroids + tocilizumab and tocilizumab alone.
Nguyen, 2021 [33]	Hospitalized pts with SARS-Cov-2 infection	No information provided	2 (6818). 1 brasilian trial (Metcovid) and 1 UK trial (Recovery [4, 5]	2	-	Methylprednisolone, dexamethasone	Standard of care	28-days mortality	Steroids reduce the risk of 28-day mortality, but the magnitude of reduction is likely modest.
Ferreto, 2021 [34]	SARS-CoV-2 infection	hospitalized SARS-CoV-2 patients.	2 (6724)	2	-	Dexamethasone	Standard of care	Mortality, hospital discharge rate.	Dexamethasone may significantly improve the outcome among hospitalized patients with SARS-CoV-2 infection
Yu, 2021 [35]	COVID-19 pts.	Sever/critical ill pts	13 (6612)	2	6 cohort studies, 5 case-control studies	Methylprednisolone, dexamethasone, hydrocortisone, and prednisone	Control group without steroids	Mortality and invasive mechanical ventilation.	Using glucocorticoids could reduce mortality and risk of progression to invasive mechanical ventilation in severe COVID-19 patients.
Sahilu, 2021 [36]	Pts. with COVID-19	Pts. with different severity of infection	32 (14,659)	4	28 retrospective or prospective cohort studies	Various steroids (methylprednisolone, hydrocortisone, dexamethasone); 1 trial use oral steroids	No information provided	death within the hospital (all-cause mortality); prevalence of severe cases in the two groups	There was no significant difference in all-cause mortality between the steroid and nonsteroid groups. There was no significant reduction of all-cause mortality in critically ill COVID-19 patients treated with corticosteroids. Higher prevalence of severe disease were observed in steroid recipients compared to controls.
Boppana, 2021 [37]	COVID-19 pts.	Pts. with different severity of infection.	6 (7707)	6	-	Steroids (hydrocortisone, methylprednisolone, dexamethasone)	Usual care or placebo	21 and 28 days mortality, adverse events	In pts, requiring mechanical ventilation, use of steroids reduces all-cause mortality.
Wagner, 2021 [38]	pts with. COVID-19	Hospitalized pts. regardless to severity, age, gender or etnicity	11 (8075, 7041 from high income countries)	11	-	3022 received steroids (2322 dexamethasone)	Standard of care	All-cause mortality, ventilator-free days, adverse events	Moderate-certainty evidence shows that systemic corticosteroids probably slightly reduce all-cause mortality in people hospitalised because of symptomatic COVID-19. Low-certainty evidence suggests that there may also be a reduction in ventilator-free days. Currently, there is no evidence for asymptomatic or mild disease (non-hospitalised participants).
Tan [39]	COVID-19 pts	hospitalized COVID-19 pts.	12 (2759 pts)	3	9	High-dose and low-dose corticosteroids.	SOT	Mortality rate; progression rate (ICU admission, respiratory support) duration of hospital stay, duration of mechanical ventilation, adverse events (incidence of hyperglycemi, infection rate).	The primary aim of this systematic review was to evaluate the use of high-dose versus low- dose corticosteroids on the mortality rate of COVID-19. The pooled analysis demonstrated no significant difference in mortality rate between the high-dose and low-dose corticosteroids groups
Chaharom [40]	COVID-19 patients	Pts with different severity of disease	29 (18,190)	6	23	Various steroids	SOT, placebo	Mortality, hospitalizatio, ICU admission, intubation, and mechanical ventilation	Steroids had no impact on mortality in the overall analysis of 18190 pts, but in subgroup analysis of RCTs decreased mortality compared to controls.. Additionally, the risk of admission to the ICU, the need for endotracheal intubation, and mechanical ventilation were comparable between patients receiving corticosteroids and controls. The duration of hospitalization was also similar in the two groups.
Caiazzo, 2022 [41]	Pts. with COVID-19, SARS, MERS or influenza.	Adult (>18 years) patients hospitalized	No RCTs of glucocorticoids for SARS, MERS or influenza reported relevant outcomes. 11 COVID-19 RCTs (8109 pts.) were included	11. The RECOVERY trial [4] contributed 80% of all patients to the meta-analysis.	-	Hydrocortisone, methylprednisolone, dexamethasone.	Placebo or standard of care	Mortality, adverse events	Administration of systemic glucocorticoids to patients hospitalised with COVID-19 does not lower mortality overall but may reduce it in those requiring respiratory support and increase it in those who do not.
Mohanty, 2022 [42]	Pts. with COVID-19	Hospitalized pts with infection from moderate to critical	12 trials (3110). 902 pts received pulse dose meth., 756 low dose steroids, 1452 usual care	1	11 cohort studies (8 retrospective)	Pulse dose methylprednisolone (≥125 mg/day for a minimum of 3 days)+ standard of care	Usual care alone or with low dose steroids (≤1 mg/kg steroids)	Mortality, adverse events	Pulse dose methylprednisolone reduced mortality compared to usual care, but no difference was found when compared to low-dose steroids.
Griesel, 2022 [43]	People with a confirmed diagnosis of asymptomatic SARS-CoV-2 infection or mild COVID-19	COVID-19, irrespective of disease severity, age, sex, or ethnicity.	3 RCTs (3017; 2490 had mild covid). No studies that included people with a confirmed diagnosis of moderate-to-severe COVID-19 were found.	3	-	Inhaled corticosteroids plus Standard of care	Standard of care (with or without placebo).	Mortality, risolution of symptoms, admission to hospital	In people with COVID-19 and mild symptoms there is moderate-certainty evidence that inhaled corticosteroids probably reduce the combined endpoint of admission to hospital or death and increase the resolution of all initial symptoms at day 14. Low-certainty evidence suggests that corticosteroids make little to no difference in all-cause mortality up to day 30 and may decrease the duration to symptom resolution.
Hong, 2022 [44]	COVID-19 patients.	Most studies were conducted in China (n=16), followed by the United States (n=5), Spain (n=5), Italy (n=3) the United Arab Emirates (2), Brazil (n=1) [and Iran (n=1). The study interval in each study ranged from 1 January 2020 to 31 July 2020. More than half of the studies recruited patients who suffered from severe or critically ill COVID-19 pneumonia	33 (4142)	5 (52)	28 (3490) observational studies	Methylprednisolone	Standard of care	Mortality, ICU admission, mechanical ventilation, viral shedding	Methylprednisolone treatment was associated with reduced short-term mortality, less need for ICU admission and mechanical ventilation , increased 28-day ventilator-free days, without increasing risk of secondary infections, but could prolong duration of viral shedding. Patients with severe COVID-19 are more likely to benefit from short-term, low-dose methylprednisolone treatment.
Thakur, 2022 [45]	COVID-19 pts	No other information available	21 (9922 patients)	13	8	Methylprednisolone, dexamethasone, hydrocortisone. 4018 were on steroids	5904 were in the nonsteroid group" (no other information available)	Mortality	There was a significant reduction in deaths of COVID19 pts. in the steroidal group as compared to the non-steroidal group. In subgroup analysis, methylprednisolone has shown a significant reduction in deaths as compared to the non-steroidal group, however, more clinical evidence is required for dexamethasone and hydrocortisone
KhoKher, 2022 [46]	COVID-19	Hospitalized pts with pneumonia of different severity.	10 (3065 pts)	-	10 observational studies	1289 received pulse dose steroids (e.g., 1 g of methylprednisolone daily.	1778 received conventional doseing, not-pulse dose steroids (NPDS)	Mortality, need of endotracheal intubation, length of hospital stay, Adverse events	Compared to Non-pulse-dose steroids, pulse dose steroids was associated with similar mortality rates, need for endotracheal intubation, length of hospital stay and adverse events

Supplemental Table 2 - Effects of corticosteroids on more commonly reported outcomes.

Review [reference]	*No. studies*	*Covid-19 pts. characteristics, No. subjects (steroids/controls)*	*Effect size (RR, OR, HR or RD) and 95% CIs*	*GRADE assessment (reasons for downgrading)*	*Comment*	*Effect size direction*
Outcome			*Mortality*			
Yousefifard [12]	15 studi (1 RCT) in COVID-19, SARS and MERS	5 cohort studies in COVID-19. 428 pts (187/241)	OR 1.08 (0.34/3.50)	Very-low (serious ROB, heterogeneity, imprecision)	It is unclear if corticosteroids reduce mortality of severe COVID-19 compared to control.	
Lee [13]	1 non-RCT in COVID-19 pts with ARDS	201 (pts. with ARDS (62/139); adjusted analysis 84 (50/34)	HR 0.38 (0.20/0.72)	⊕⊕⊕⊖ Moderate (imprecision)	After adjustment for time and comorbidity, steroids use reduces mortality compared to controls in ARDS pts	
Li [14]	10 non-RCT, 1 RCT	No separate data for Covid-19 pts available	No separate data for COVID-19 pts available			na
Yang [15]	2 non-RCTs	179 (71/108)	No separate outcome data for Covid-19 pts available		Pts. with severe conditions are more likely to require corticosteroids	na
Cantini [16]	1 RCT (Recovery trial) [4]	Pts. with different severity of illness. 6325 (2104/4321)	- No O_2 need : RR 1.22 (0.93/1.61). - O_2 need: RR 0.80 (0.70/0.92). - Ventilated pts: RR 0.65 (0.51/0.82)	⊕⊕⊕⊖ Moderate (ROB due to deviation from intended intervention)	Steroids reduce mortality compared to controls in ventilated pts and in pts requiring O2 supplementation, but not in pts not requiring O_2 supplementation	
Cheng [17]	20 non-RCTs (2840)	Mortality data available from 6 reports (2349 pts). Pts with different severity of infection	- RR 1.59 (0.69/3.66) in the overall analysis. - RR 1.80 (0.51/6.33) in severe case	⊕⊖⊖⊖ Very low (serious ROB, heterogeneity, imprecision	The use of steroids did not reduce mortality compared to controls	
Wang [18]	16 (3285) mostly from case series and case reports	Mortality data available from 4 reports (495). Pts with different severity of illness	RR 1.38 (0.87/2.18)	⊕⊖⊖⊖ Very low (serious ROB, heterogeneity, imprecision)	Severe pts. were found to be more likely requiring corticosteroids therapy.	
Sarma [19]	15 (3 RCTs, 12 cohort studies)	Mortality data in severe/critical pts. from 6 observational studies (5787 pts, and in mild/moderate pts from 2 studies (1566 pts)	- Severe/critical pts. RR 0.83 (0.76/0.91) - Mild/moderate, RR 1.27 (1.0/1.61)	⊕⊕⊕⊖ Moderate (ROB) ⊕⊕⊖⊖ Low (ROB, imprecision)	Steroids reduce mortality compared to controls in severe/critical ill pts., but not in mild/moderate pts.	
Tlayjek [20]	20 (16977 pts), including one RCT (Recovery trial) [4] and 19 non RCTs.	Ten studies (1 RCT, 9 cohorts) evaluated short term mortality in 10278 pts	RR 0.91 (0.71/1.16)	⊕⊖⊖⊖ Very low (serious ROB, heterogeneity, imprecision)	The pooled analysis of 1 RCT and 9 observational studies shows that steroids use is not associated with reduction in short-term mortality across all the disease severity groups (critical, severe, and non severe ill pts.)	
WHO [21]	7 RCTs (1703 pts)	Mortality data reported in critical ill pts. who were and were not receiving invasive mechanical ventilation at randomization. 1703 pts (678/1025)	OR 0.66 (0.53/0.87)	⊕⊕⊕⊕ High (based on RCTs without important limitations).	In critically ill pts. administration of systemic corticosteroids, compared with usual care or placebo was associated with lower 28-day all-cause mortality.	
Ye [22]	The review included a variety of studies in patients with COVID-19, severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), influenza, ARDS, CAP[a]	Data on COVID-19 pts limited to 2 observational studies of 331 pts. with severe COVID-19, and 1 observational study in ARDS pts	- HR 2.30 (1.00/ 5.29) Severe infections - HR 0.41 (0.20 /0.83) ARDS pts	⊕⊖⊖⊖ Very low (ROB, serious imprecision)	Basing on direct evidence it appears that corticosteroids may increase mortality compared with no corticosteroids in pts with severe infection, and decrease mortality in pts with ARDS	
Van Paassen [23]	44 studies (5 RCTs, 39 non-RCTs) for a total of 20.197 pts, with severity of infection ranging from need of hospitalization to admission to ICU	22 studies (14187 pts) reported mortality data	- OR 0.72 (0.46-0.97) Observational studies - OR 0.89 (0.69 /0.99) RCTs	⊕⊕⊖⊖ Low (ROB, heterogeneity) ⊕⊕⊕⊖ Moderate (ROB)	Both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality in pts requiring hospitalization or ICU admission.	
Chauduri [24]	18 RCTs (2826 pts) in pts with ARDS of any ethiology	8 RCTs in 1700 (700/1041) covid-19 pts	RR 0.82 (0.72 to 0.95)	⊕⊕⊕⊖ Moderate (indirectness)	Results from 16 RCTs in ARDS pts show a decrease of mortality in steroids recipients. Subgroup analysis based on COVID-19 status, steroid type, steroid initiation time, steroid dosage, and ROB did not demonstrate any credible subgroup effect, Patients who received a longer course of corticosteroids (over 7 days) had higher rates of survival than those who received a shorter course (<7 days).	
Hasan [25]	5 RCTs	Pts with various severity of covid-19 (652 pts)	OR 0.64 (0.29/1.43)	⊕⊕⊖⊖ Low (ROB, heterogeneity)	Low dose methilprednisolone did not reduce mortality compared to controls.	Mettere dopo
Ma [26]	7 RCTs	Mostly pts with severe disease. 6250 pts (2385/3865)	RR: 0.85 (0.73–0.99).	⊕⊕⊖⊖ Low (serious ROB, including suspected publication bias)	Steroids reduce mortality compared to controls	
Pasin [27]	5 RCTs	Pts with different severity of disease. 7692 pts (2835/4857).	- RR 0.39 (0.87/0.96) overall analysis	⊕⊕⊕⊖ Moderate (ROB)	Mortality in pts. treated with steroids was slightly but significantly lower than mortality of controls. The same beneficial effect was found in the subgroup of patients requiring mechanical ventilation Remarkably, steroids increased mortality in the subgroup of patients not requiring oxygen	
		1417 (529/888) requiring mechanical ventilation.	- RR 0.85 (0.72/1.00) Pts on MV	⊕⊕⊖⊖ Low (ROB, inconsistency)		
		1607 (531/1076) not requiring O2 supplementation	- RR 1.28 (1.00/1.62)	⊕⊕⊖⊖ Low (ROB, imprecision)		
Pulakulthri [28]	8 RCTs,	Pts with different severity of disease. 7737 pts (2795/4942)	OR 0.85 (0.76/0.95)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Steroids reduce the odds for mortality.	
Sahu [29]	7 trials (4 RCTs, 3 observational) for a total of 2214 pts	Pts. not requiring oxygen supplementation	OR 1.35 (1.01/1.79)	⊕⊕⊖⊖ Low (serious ROB)	In pts not requiring oxygen supplementation, steroids increases mortality comparede to SOT	
Tu [30]	10 RCTs for a total of 12473 pts	Hospitalized pts, all (4354/8119)	- RR 0,93 (0.82/1.05)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Steroids did not reduce mortality compared to control, even in pts requiring mechanical ventilation However, in pts not requiring oxygen supplementation, steroids increases mortality compared to SOC	
		- Pts requiring mechanical ventilation, 5 trials, 2234 pts. (803/1431)	- RR 0.90 (0.79/1.02)			
		- Pts not requiring oxygen supplementation. 4 trials, 2769 pts (918/1851)	- RR 1.23 (1.03/1.47)			
Cano [31]	33 studies in the quantitative synthesis	33 studies (1 RCT), 13564 pts (4919/8735) in the overall analysis	OR 2.30 (1.45/3.63)	⊕⊖⊖⊖ Very low (serious ROB, inconsistency)	Overall mortality of pts receiving steroids was higher than in patients not receiving steroids, with the caveat that the population studied was too heterogeneous, possibly because of selection bias among studies, with corticosteroids administered to patients with grave prognosis at baseline. On the other hand, there was moderate evidence of mortality benefit in severely ill patients treated with steroids	
		8 trial, 1404 pts (564/840) in severly ill pts	OR 0.65 (0.51/0.83)	⊕⊕⊕⊖ Moderate (ROB)		
Moosazadeh [32]	5 cohort studies comparing steroids + tocilizumab vs standard of care or tocilizumab alone	No information of COVID-19 severity provided. 460 pts received corticosteroids and tocilizumab and 303 tocilizumab alone. In the comparison with standard of care group, 567 pts received corticosteroids and tocilizumab, and 890 standard of care	- Steroids+tocilizumab vs tocilizumab alone, 0.74 (0.36/1.50) - Steroids+ tocilizumab vs standard of care 0.48 (0.31–0.74.)	⊕⊖⊖⊖ Very low (ROB, indirectness, inconsistency)	The risk of death in the group of corticosteroids and tocilizumab was similar to the tocilizumab alone group. But was significantly lower in patients who received corticosteroids and tocilizumab compared to the control group.	
Nguyen [33]	2 RCT (6818 COVID-19 pts).	Hospitalized pts. with different severity of COVID-19. Data from Recovery and Metcovid trials [4,5]; 6818 pts (2298/4520)	RR 0.90 (0.83/0.98).	⊕⊕⊕⊖ Moderate (ROB)	Based on this Bayesian meta-analysis,, steroids reduces the risk of 28-day mortality compared to controls	
Ferreto [34]	2 RCTs (6724)	Hospitalized pts. with different severity of COVID-19. 6724 pts (2255/4469)	RR 0.89 (0.82/0.97)	⊕⊕⊕⊖ Moderate (ROB)	Treatment with dexamethasone had a positive impact on mortality and length of hospitalization among SARS-CoV-2 hospitalized pts.	
Yu [35]	13 studies (2 RCTs, and 11 cohort/case control studies)	6612 confirmed severe COVID-19 pts	HR 0.60 (0.45/0.79)	⊕⊕⊕⊖ Low (ROB, heterogeneity)	Steroids reduce mortality (and risk of progression to invasive mechanical ventilation) in severe COVID-19 pts.	
Sahilu [36]	32 studies (5 RCTs and 27 non-RCTs)	14659 pts (5830/8829) with different severity of COVID-19. Pts, with severe conditions were more likely receiving corticosteroids.	- In the overall analysis, RR 0.95 (0.80/1.13). - In critically ill pts, RR 0.89 (0.62/1.27)	⊕⊖⊖⊖ Very low (ROB, imprecision, inconsistency)	No significant differences in mortality between the corticosteroid and noncorticosteroid treatment groups were observed in the overall population and critical ill pts.	
Boppana [37]	6 RCTs (*710*7 pts.	- In the overall analysis (6 trials), OR 0.76 (0.53 /1.00); - In pts. requiring 02 or IMV (6 trials), OR 0.74 (0.57 /0.97) - In pts. not requiring 02 or IMV (1 trial), OR 1.32 (0.99/1.77)	⊕⊕⊖⊖ Low (ROB, heterogeneity) ⊕⊕⊕⊖ Moderate (inconsistency) ⊕⊖⊖⊖ Very low (ROB, serious imprecision)	Steroids reduce mortality in pts requiring 02 supplementation or invasive mechanical ventilation, but not in pts. not requiring 02 supplementation		
Wagner [38]	11 RCTs (8075 pts)	8075 pts (3072/5003) with different severity of COVID-19	RR 0.89 (0.80/1.00)	⊕⊕⊕⊖ Moderate (ROB)	Systemic steroids reduces mortality slightly	
Chaharom [40]	29 studies (18190 pts)	Hospitalized pts with different severity of infections	OR 1.12 (0.83/1.50) - Overall analysis	⊕⊖⊖⊖ Very low (serious ROB, inconsistency)	Compared to controls, steroid treatment had no impact on mortality in the overall analysis, but decreased mortality in subgroup analysis of RCTs	
			OR 0.84 (0.75/0.94) In 6 RCTs, 7717 pts	⊕⊕⊕⊖ Moderate (ROB)		
Caiazzo [41]	11 RCTs (8109 patients)	Pts with different severity of COVID-19	- Mortality at longest follow-up, RR 0.87 (0.74 /1.03). - Mortality at 14 days, RR 0.81 (0.69 /0.85).	⊕⊕⊖⊖ Low (ROB, inconsistency)	Systemic glucocorticoids might reduce mortality at 14 days follow-up. With longer follow-up, administration of glucocorticoids was associated with a trend to benefit for those requiring mechanical ventilation but possible harm for those not receiving oxygen at randomisation	
Mohanty [42]	12 studies (1 RCT, 11 observational studies)	3110 pts from 9 trials 902 received pulse-dose steroids, 756 low-dose steroids, 1452 usual care without steroids); pts. with different severity of COVID-19.	- Pulse dose methylprednisolone vs usual care: OR 0.71 (0.51 /0.97) - Pulse dose methylprednisolone vs low-dose steroids: OR 0.669(.44 /1.01)	⊕⊕⊕⊖ Moderate (ROB) ⊕⊕⊖⊖ Low (ROB, imprecision)	The review shows a significant reduction of all cause mortality in pulse-dose steroids compared to usual care, but it is unclear whether pulse-dose steroids reduces mortality compared to low-dose steroids	
Griesel [43]	3 RCTs	Asymptomatic SARS-CoV-2 infection or mild COVID-19; 2132 pts (1057/1075)	-RR 0.61 (0.22/1.67)	⊕⊕⊖⊖ Low (serious imprecision)	it is unclear whether inhaled steroids + standard of care reduces mortality compared to standard of care alone.	
Hong [44]	33 trials (5 RCTs)	More than half of the studies recruited pts who suffered from severe or critically ill COVID-19	-in the overall analysis (non-RCTs and RCTs), RR 0.73 (0.60/0.89) -in 5 small size RCTs, RR 0.81 (0.50/1.31)	⊕⊕⊖⊖ Low (ROB, inconsystency) ⊕⊕⊖⊖ Low (imprecision, inconsystency)	Methylprednisolone treatment is associated with reduced short-term mortality, but the benefit is not clear when the analysis is limited to RCTs	
Thakur [45]	21 (13 RCTs, 8 non-RCTs)	9922 pts (4018/5904), with different severity of COVID-19	OR 0.52 (0.34, 0.80)	⊕⊕⊖⊖ Low (ROB, inconsystency)	There was a significant reduction in deaths of COVID-19 patients in the steroidal group as compared to the non-steroidal group	
Khokher [46]						
Outcome			*Adverse events*			
Yang[15]	hyperglicemia	2 non-RCTs trials, 179 pts (71/108)	RR 1.37 (0.68/2.76)	⊕⊖⊖⊖ Very-low (serious ROB, imprecision)	There was no relationship between corticosteroid use and the development of hyperglicemia	
	Bacterial infections		RR 2.08 (1.54/2.81)	⊕⊕⊖⊖ Very-low (serious ROB, imprecision)	Pts. treated with corticosteroids were more likely to have bacterial infectios compared to controls	
Tlayjek [20]	Acquired bloodstream infections	78 pts. from 1 observational study	HR 3.95 (1.20/13.03)	⊕⊖⊖⊖ Very-low (ROB,serious imprecision).	Pts. treated with corticosteroids were more likely to have bloodstream infections compared to controls	
WHO [21]	Serious Adverse events	6 RCTs, 796 pts (354/342)	RR 0.77 (0.58/1.04)	-⊕⊕⊖⊖ Low (ROB, inconsystency)	No significant differences in the occurrence of adverse events in steroids recipients compared to controls	
Chaduri [24]	hyperglicemia	6 RCTs (3 in covid-19 pts), 915 pts (480/435)	RR 1.11 (1.01/1.23)	⊕⊕⊕⊖ Moderate (indirectness due to variability in definition of hyperglicemia)	Slightly increase of glicemia in steroids recipients compared to controls	
	Gastrointestinal bleeding	436 pts (217/219)	RR 1.20 (0.43/3.34)	⊕⊕⊖⊖ Low (ROB, inconsystency)	Unclear differences between groups	
Griesel [43]	Serious Adverse events	1 trial, 1586 pts (787/799)	RR 0.78 (0.47/1.31)	⊕⊖⊖⊖ Very-low (ROB, serious imprecision	It is unclear wheter steroids increases serious adverse events compared to controls	
	Any Adverse event	1 trial, 400 pts (197/203)	RR 0.78 (0.41/1.31)	⊕⊕⊖⊖ Low (serious imprecision)	It is unclear wheter steroids increases overall adverse events compared to controls	
	Infections		RR 0.88 (0.30/2.58)		It is unclear wheter steroids increases 2y infections compared to controls	
Hong [44]	2y infections	Low-dose steroids, 8 trials, 748 pts (383/335)	RR 1.17 (0.89/0.54)	⊕⊖⊖⊖ Very-low (ROB, inconsistency, imprecision)	It is unclear wheter steroids , both at low or high-dose,increase 2y infections compared to controls	
		High-dose steroids, 3 trials, 368 pts (173/195)	RR 0.81 (0.51/1.30)			
Ma [26]	Serious Adverse events	4 RCTs, 898 pts (539/359)	RR 1.16 (0.39/1.43)	⊕⊕⊖⊖ Low (serious ROB, including suspected publication bias)	Unclear differences between groups	
Pulakurthi [28]	Serious adverse events	4 RCTs , 748 pts (398/350)	OR 1.09 /0.37/3.33)	⊕⊕⊖⊖ Low (ROB, imprecision)	Similar rates of serious adverse events and infectious complications among steroids recipients and controls	
	superinfection	3 RCTs, 510 pts (261/249)	OR 0.75 (0.50/1.13)			
Tu [30]	Adverse events	7 RCTs, 3050 pts (1208, 1842)	RR 1.13 (0.58./2.28)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Unclear differences between groups	
	Secondary infections	4 trials, 140 pts (66/74)	RR 0.87 (0.66/1.15)			
Outcome			*Viral clearance*			
Cheng [17]	4 cohort studies	247 pts	MD 1.01 (-0.91/2.02)	⊕⊖⊖⊖ Very-low (ROB, inconsistency, imprecision)	Viral clearance is not delayed in steroids recipients compared to controls	
Sarma [19]	1 non-RCT	64 pts (41/28)	MD -1.63 (-4.84/1.58)	⊕⊕⊖⊖ Very-low (ROB, serious imprecision)	Viral clearance is not delayed in steroids recipients compared to controls	
Tlayjek [20]	6 observational studies	760 pts	RR 1.47 (1.11/1.93	⊕⊖⊖⊖ Very-low (serious ROB, inconsistency)	Viral clearance is delayed in steroids recipients compared to controls	
Hong [44]	13 trials	1069 (455/614)	MD 1.03 (0.25/1.82)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Viral clearance is not delayed in steroids recipients compared to controls	
Sahu [29]	5 trials (1 RCT)	597 pts (297/300)	MD 0.20 (0.04/0.36)	⊕⊖⊖⊖ Very-low (serious ROB, inconsistency)	Viral clearance is delayed in controls compared to steroids	
Outcome			*Progression of disease (requirement of ICU, need for invasive mechanical ventilation)*			
Sarma [19]	2 non-RCTs	386 pts (215/171)	0.62 (0.45/0.86)	⊕⊕⊕⊖ Moderate (ROB)	Steroids reduce requirement of ICU compared to controls	
	6 trials (1 RCT)	1338(558/780)	0.59 (0.51/0.69)	⊕⊕⊕⊖ Moderate (ROB)	Steroids reduce requirement of mechanical ventilation compared to controls	
Tlayjek [20]	3 trials (1 RCT, 2 non.RCTs)	5785 pts	RR 0.74 (0.50/1.09)	⊕⊕⊖⊖ Low (ROB, inconsistency)	It is unclear if corticosteroids, compared to controls, reduce the need of invasive mechanical ventilation in pts. with severe COVID-19	
Van Paassen [23]	7 trials (2 RCTs)	939 pts (467/472)	OR 0.70 (0.54/0.91)	⊕⊕⊖⊖ Low (serious ROB)	Steroids reduce requirement of mechanical ventilation compared to controls	
Yu [35]	3 trials (1 RCT, 2 non-RCTs)	1572 pts	RR 0.69 (0.58/,0.83)	⊕⊕⊖⊖ Low (serious ROB)	Steroids reduce requirement of mechanical ventilation compared to controls	
Wagner [38]	1 RCT	86 pts	RR 0.48 (0.23/1.00)	⊕⊕⊖⊖ Very-low (ROB, serious imprecision)	Steroids may reduce need for invasive mechanical ventilation compared to controls	
Mohanty [42]	- Pulse dose steroids vs standard of care	5 trials , 1584 pts (566/1018)	OR 0.69 (0.53/0.91)	⊕⊕⊕⊖ Moderate (ROB)	Steroids reduce requirement of invasive mechanical ventilation compared to controls	
Ma [26]	4 RCTs	4161 (1464/2697)	RR 0.85 (0.77–0.93)	⊕⊕⊖⊖ Low (serious ROB, including suspected publication bias)	Steroids decreased the occurrence of composite disease progression compared to controls	
Pasin [27]	3 RCTs	6873 (2329/4544)	RR 0.75 (0.60/0.94)	⊕⊕⊕⊖ Moderate (ROB)	Steroids decrease the need for mechanical ventilation	
Pulakurthi [28]	5 RCTs	5785 /1979/3806)	OR 0.76 (0.59/0.97)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Steroids reduce the odds for need of mechanical ventilation compared to controls	
Sahu [29]	2 non-RCTs	180 (90/90)	OR 5.97 (1.27/27.99)	⊕⊖⊖⊖ Very-low (serious ROB, serious imprecision)	In pts not requiring oxygen supplementation steroids increase rate of progression of disease compared to controls	
Tu [30]	7 RCTs	9771 pts (3298/6473)	RR 0.82 (0.62/1.08)	⊕⊕⊖⊖ Low (ROB, inconsistency)	It is unclear if steroids reduce the need for mechanical ventilation compared to controls	
Charon [40]	Need for mechanical ventilation, 14 studies (5 RCTs)	9416 (3546/5870)	OR 1.21 (0.79/1.85)	⊕⊕⊖⊖ Low (ROB, inconsistency)	It is unclear if steroids reduce the need for mechanical ventilation compared to controls	
	ICU admission, 11 studies (2 RCTs)	3730 pts (1527/2203)	OR 1.43 (0.79/1.58)	⊕⊕⊖⊖ Low (ROB, inconsistency)	It is unclear if steroids reduce rate of ICU admission compared to controls	
Outcome			*Length of hospital stay (LOS)*			
Cheng [17]	3 cohort studies	290 pts	MD -3.17 (-7.37/1.04)	⊕⊕⊖⊖ Low (ROB, imprecision)	It is unclear if steroids reduces LOS compared to controls.	
Chaduri [24]	4 RCTs	344 pts (188/156)	MD -8.05 (-12.98/-3.12)	⊕⊕⊖⊖ Low (serious ROB)	Corticosteroids reduce LOS compared to controls	
Sahu [29]	4 trials (1 RCT, 3 non-RCTs)	345 pts (171?174)	MD 0.83 (0.61/1.05)	⊕⊕⊖⊖ Low (serious ROB)	It is unclear if steroids reduce LOS compared to controls.	
Charom [40]	12 studies (1 RCT)	4377 pts (1743/2634)	OR 1.56 (0.29/3.41)	⊕⊕⊖⊖ Low (ROB, inconsistency)	It is unclear if steroids reduce LOS compared to controls	
Subgroup analysis according to steroid regimens						
Mortality						
Khokher [46]	10 observational trials comparing non-pulse dose and pulse-dose steroids	809 pts (388/421)	RR 1.23 (0.92/1.65)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Compared to non-pulse dose steroids, pulse-dose steroid therapy was associated with similar mortality rates,	
Hong [44]	5 trials with low-dose methilprednisolone vs SOC	586 pts (316+270)	RR 0.59 (0.44/0.80)	⊕⊕⊖⊖ Low (serious ROB)	Low-dose methilprednisolone reduces mortality compared to SOC	
	3 trials with high dose methilprednisolone vs SOC	724 pts (326/398)	RR 0.89 (0.74/1.06)	⊕⊕⊖⊖ Low (serious ROB)	It is unclear if high dose methilprednisolone reduces mortality compared to SOC	
Tu [30]	8 RCTs with low-dose steroids vs SOC	7695 pts (2759/4936)	RR 0.90 (0.83/0.97)	⊕⊕⊕⊖ Moderate (ROB)	Low-dose steroids reduce mortality compared to SOC	
	3 RCTs Dexamethasone vs SOC	6774 pts (2280/4494)	RR 0.86 (0.76/0.97)	⊕⊕⊕⊖ Moderate (ROB)	Low-dose dexamethasone reduces mortality compared to SOC	
Cano [31]	14 studies with low-dose steroids vs SOC	7564 pts (2828/4736)	OR 1.13 (0.71/1.80)	⊕⊖⊖⊖ Very-low (serious ROB, inconsistency)	It is unclear if low-dose steroids reduce mortality compared to SOC	
	2 studies with high-dose steroids vs SOC	245 pts (169/76)	OR 0.57 (0.27/1.23)	⊕⊕⊖⊖ Low (ROB, imprecision)	It is unclear if high-dose steroids reduce mortality compared to SOC	
Tan [39]	11 studies (3 RCTs) comparing high-dose vs low-dose steroids	2632 pts (1064/1568)	OR 1.07 (0.67/1.72)	⊕⊖⊖⊖ Very-low (serious ROB, inconsistency)	It is unclear if high-dose steroids reduce mortality compared to low-dose steroids	
	4 studies comparing high-dose methilprednisolone vs low-dose dexamethasone	1091 pts (406/685)	OR 0.84 (0.34/2.07)	⊕⊖⊖⊖ Very-low (serious ROB, inconsistency)	It is unclear if high-dose methilprednisolone reduce mortality compared to low-dose daxamethasone	
Adverse events						
Tan [39]	Hyperglicemia, 3 trials	516 pts (268/248)	OR 0.91 (0.58/1.43)	⊕⊕⊕⊖ Moderate (imprecision)	No clear differences in the occurrence of hyperglicemia in high-dose vs low-dose steroids recipients	
	2y infections, 5 studies	1485 pts (645/840)	OR 0.86 (0.64/1.16)	⊕⊕⊕⊖ Moderate (imprecision)	No clear differences in the occurrence of secondary infections in high-dose vs low-dose steroids recipients	
Nedd for mechanical ventilation, admission to ICU						
Khokher [46]	4 observational trials comparing non-pulse dose vs pulse-dose steroids	1729 pts (738/691)	RR 0.71 (0.37/1.37)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Rates of pts requiring mechanical ventilation were similar among pts receiving non-pulse-dose steroids, and those receiving pulse-dose therapy.	
Hong [44]	6 trials with low-dose methilprednisolone	666 pts (351/305)	RR 0.55 (0.39/0.76)	⊕⊕⊖⊖ Low (serious ROB)	Low-dose methilprednisolone reduces need for mechanical ventilation compared to SOC	
	3 trials with high dose methilprednisolone	202 pts (67/135)	RR 0.80 (0.63/1.02)	⊕⊕⊖⊖ Low (serious ROB)	It is unclear if high dose methilprednisolone reduces the need for mechanical ventilation compared to SOC	
Mohanti [42]	3 trials comparing low-dose vs pulse dose steroids	711 pts (333/378)	RR 0.98 (1.63/1.52)	⊕⊕⊖⊖ Low (ROB, inconsistency)	Rates of pts requiring mechanical ventilation were similar among pts receiving low-dose steroids, and those receiving pulse-dose steroids	
Tan [39]	7 studies comparing low- and high-dose steroids	1544 pts (663/881)	OR 0.77 (0.43/1.37)	⊕⊖⊖⊖ Very-low (serious ROB, inconsistency)	Rates of pts admitted to the ICU were similar between low-dose and high-dose steroids recipients	
Length of hospital stay						
Khokher [46]	3 trials comparing non-pulse vs pulse-dose steroids	781 pts (372/409)	MD 1.03 (-1.46/5.33)	⊕⊕⊖⊖ Low (ROB, inconsistency)	LOS was similar among pts receiving non-pulse-dose steroids, and those receiving PDT	
Tan [39]	7 studies comparing low-dose vs high-dose steroids	1615 pts (651/964)	MD 0.53 (-1.36/2.41)	⊕⊖⊖⊖ Very-low (serious ROB, inconsistency)	LOS was similar among pts receiving low-dose steroids, and those receiving high-dose steroids	

Footnotes. RCT, randomized clinical trial; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; pts, patients; OR, odds ratio; RR, risk ratio; RD, risk difference; HR, hazard ratio; ROB, Risk of bias; SOC, standard of care. ICU, intensive care unit; LOS, length of hospital stay.

The effect size favours steroids compared to controls in a significant way.

No significant differences between groups.

The effect size favours controls compared to steroids in a significant way.