Global Epidemiology 6 (2023) 100116

Contents lists available at ScienceDirect

Global Epidemiology

journal homepage: www.sciencedirect.com/journal/global-epidemiology

Comparison of corticosteroids types, dexamethasone, and methylprednisolone in patients hospitalized with COVID-19: A systematic review and network meta-analysis

Mina Morsali [a], Amin Doosti-Irani [a,*], Shahideh Amini [b], Maryam Nazemipour [c], Mohammad Ali Mansournia [c,**], Rasoul Aliannejad [d,e]

[a] Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
[b] Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[d] Division of pulmonary and critical care, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[e] Advanced Thoracic Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
COVID-19
Dexamethasone
Hydrocortisone
Methylprednisolone
Network meta-analysis

ABSTRACT

Background: COVID-19 is associated with severe pneumonia lung damage, acute respiratory distress syndrome (ARDS), and mortality. In this study, we aimed to compare corticosteroids' effect on the mortality risk in patients hospitalized with COVID-19.

Methods: PubMed, Web of Science, Scopus, Cochrane Library, and Embase, were searched using a predesigned search strategy. Randomized controlled trials (RCTs) that had compared the corticosteroid drugs were included. The hazard ratio (HR) with a 95% confidence interval (CI) was used to summarize the effect size from the network meta-analysis (NMA).

Results: Out of 329 retrieved references, 12 RCTs with 11,455 participants met the eligibility criteria in this review. The included RCTs formed one network with six treatments. In addition, five treatments in two RCTs were not connected to the network. Methylprednisolone + usual care (UC) versus UC decreased the risk of death by 0.65 (95% CI: 0.47, 0.90). Among treatments in the network the highest P-score (0.89) was related to Methylprednisolone + UC.

Conclusion: Based on the results of this NMA it seems Methylprednisolone + UC to be the best treatment option in patients with COVID-ARDS and COVID pneumonia.

Introduction

Acute respiratory failure is a major cause of intensive care unit (ICU) admission for patients with COVID-19 [1]. In the absence of a specific intervention, the treatment of COVID-19 relies on relieving symptoms and organ support. The potential shorter recovery associated with remdesivir, an antiviral drug, was not observed in the subgroup of critically ill patients [3]. Until recently, no drugs have been approved to improve the survival of patients with COVID-19 and acute respiratory distress syndrome (COVID-ARDS) and COVID pneumonia [4].

Although the pathophysiology of COVID-19 is incompletely understood, the organ damage, especially diffuse lung injury, are due to both the direct cytotoxicity of the virus and dysregulated immune response. The cytokine storm in patients with COVID-19 has been discussed in the literature [5–8]. It is clear that excessive inflammation plays a main role in development of the pulmonary disease [9]. Immunomodulatory drugs, such as corticosteroids, are being investigated as the therapeutic option treatments for patients with COVID-19 [2].

Corticosteroids may impair the immune system [10]. Results of a randomized, open-label trial showed that dexamethasone in patients receiving invasive mechanical ventilation results in lower 28-day mortality than patients who received the usual care [11]. Data from a large

* Corresponding author at: Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.
** Corresponding author at: Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, PO Box: 14155-6446, Tehran, Iran.
E-mail addresses: a.doosti@umsha.ac.ir (A. Doosti-Irani), mansournia_ma@sina.tums.ac.ir (M.A. Mansournia), Aliannejad@tums.ac.ir (R. Aliannejad).

https://doi.org/10.1016/j.gloepi.2023.100116
Received 29 April 2023; Received in revised form 10 July 2023; Accepted 27 July 2023
Available online 31 July 2023

RCT using dexamethasone at 6 mg once daily for 10 days (RECOVERY trial) point to a mortality benefit, mostly in critical COVID-19 patients [12]. As with dexamethasone, methylprednisolone also has minimal mineralocorticoid activity, preventing potential safety problems with fluid retention (sodium/water imbalance), a common feature of severe ARDS [13]. Low-dose hydrocortisone, compared to the placebo, usually did not have a significant effect on people with ARDS for 21 days [4].

Up to now, various corticosteroid drugs have been suggested for patients with COVID-ARDS and COVID pneumonia. The randomized controlled trials (RCTs) have examined a variety of corticosteroid drugs such as dexamethasone, hydrocortisone, and methylprednisolone to assess the survival of patients with COVID-ARDS. However, we do have no access to RCTs, which compared all corticosteroid drugs simultaneously. In addition, some of these drugs were not directly compared in an RCT. Network meta-analysis (NMA) with a simultaneous comparison of available treatments can produce the highest level of evidence and ranking of the treatments in terms of their effectiveness [14,15]. In this systematic review and NMA, we aimed to simultaneously compare the corticosteroid types of drugs on the mortality of patients with ARDS and pneumonia caused by COVID-19.

Methods

Search strategy

The international databases including Medline, Web of Science, Scopus, Cochrane Library, and Embase were searched until 28 May 2022. We developed a search strategy to find the published RCTs that had evaluated the effect of corticosteroid drugs in patients with COVID-19 (Supplementary file). In addition, the reference list of the included RCTs was scanned and we contacted the corresponding authors of them.

Selection criteria

Type of studies and population

In this study, we included only RCTs, regardless of their language, that evaluated the corticosteroid drugs in patients hospitalized with COVID-19. The same study treatment interventions in the included studies were merged. In this study usual care, standard care, and placebo were merged and considered as usual care.

Data extraction and management

Two reviewers (MM and ADI) were responsible for screening the retrieved references. To detect and remove duplicated studies all retrieved studies were imported into EndNote software. The remained were screened based on the title and abstract. Then, the full text of the selected RCTs were reviewed based on the eligibility criteria. The information extracted were as follows: i) name of the first author, year of publication, study location, study population, sample size, follow-up time, and the approach used for analyzing i.e., intention-to-treat (ITT) or per-protocol (PP), ii) the exact type of the corticosteroid drug as an intervention as well as its dosage in each RCT arm, iii) The potential effect modifiers such as gender and mean age of participants, and iv), The outcomes including the mortality proportion (risk of death) in each arm, along with risk ratio or hazard ratio (HR) with 95% confidence interval (CI). The usual care and placebo were merged as usual care in data analysis.

Risk of bias assessment

The Cochrane tool was used for assessing the risk of bias which includes the following six items: random sequence generation, allocation concealment, blinding of outcome assessors, participants, and personnel, incomplete outcome data, and selective reporting [16,38]. The included RCTs were low risk of bias if all mentioned items were met, intermediate risk of bias if one item was not met, and were high risk if more than one items were not met.

Transitivity and consistency assumptions

The similarity was evaluated in terms of the clinical and epidemiological characteristics of patients. Our evaluation was based on characteristics of patients such as age distribution and other comorbidities. The heterogeneity was assessed through chi-square test by pairwise comparisons in the networks of interventions and it was quantified by I^2 statistics. The loop-specific and design-by-treatment interaction approaches were used to assess the consistency assumption [14,17,18]. The treatments in each network were presented visually by network plot [19]. The restricted maximum likelihood estimator was used to calculate the between-study variance [20]. The HR was used to summarize the treatment effects. A frequentist-based approach was applied for data analysis.

To rank the treatments in the network, we calculated the P-score. The P-score for each treatment in a network is calculated by using the one-sided *p*-value of rejecting the null hypothesis (Pj), and it is the mean of all 1-P[j]. The range of the P-score is between zero and one. The closer the P-score value is to one, the higher the rank of the treatment [21].

The Stata 14.2 (Stata Corp, College Station, TX, USA) was used to draw the network of treatments. All statistical analyses were conducted using R version 4.0.0 (2020-04-24). The Dersimonian-Laird random-effects model was used to estimate the direct and indirect effect sizes [20]. In this model, the direct treatment effect estimates were based on the common study variance from the NMA. The *netmeta* package was used for the network meta-analysis. The Review Manager 5.4 was used for risk of bias assessment [17].

Results

Out of 329 retrieved references, 12 RCTs with 11,455 participants were met the eligibility criteria [4,11,13,22–30] (Fig. 1). The included studies involved 12 treatments, 14 pairwise comparisons, and 10 design. The characteristics of included studies presented in the Table 1. The results of the risk of bias assessment have been shown in the Fig. 2, in addition the results of the risk of bias assessment for each study based on the items of the Cochrane risk-of-bias tool were reported in supplementary Fig. 1. The graphical presentation of treatments showed that, five treatments in two RCTs were not connected to network, therefore were excluded from NMA (Supplementary Fig. 2). The network of treatments that included in the NMA is shown in Fig. 3.

The included RCTs in the network involved 10 RCTs with six treatments and six design. It seems the similarity assumption in terms of clinical and epidemiologic features was met for participants of RCTs that were included in the NMA. Based on our evaluation, this assumption was not met for Yu et al. [30] therefore we excluded this study from NMA. The participants in this study were suspected of COVID-19 aged 50 years or older with comorbidities, and not admitted to the hospital. Based on the results of this RCT, inhaled budesonide versus usual care improves time to recovery and reduced the risk of hospitalization or death. Based on the results of consistency test assumption, there was no statistically significant difference between direct and indirect estimates of HRs (Fig. 4). The *p*-values for tests of heterogeneity (within designs) and inconsistency (between designs) were 0.0432 and 0.508 respectively. The value for I^2 for network of treatments was 49.5%.

Based on the results of NMA, Methylprednisolone + usual care (UC) versus UC decreased the risk of death (HR = 0.65; 95% CI: 0.47, 0.90). In addition, HR estimate for Budesonide versus UC was 0.78 (95% CI: 0.48, 1.26), the results were compatible with both protective and risk effects [39–41]. In terms of the ranking of treatments, Methylprednisolone +UC revived the highest score (P-score = 0.89) among the treatments in network (Fig. 5). Simultaneous comparisons of all treatments in the network are shown in Table 2.

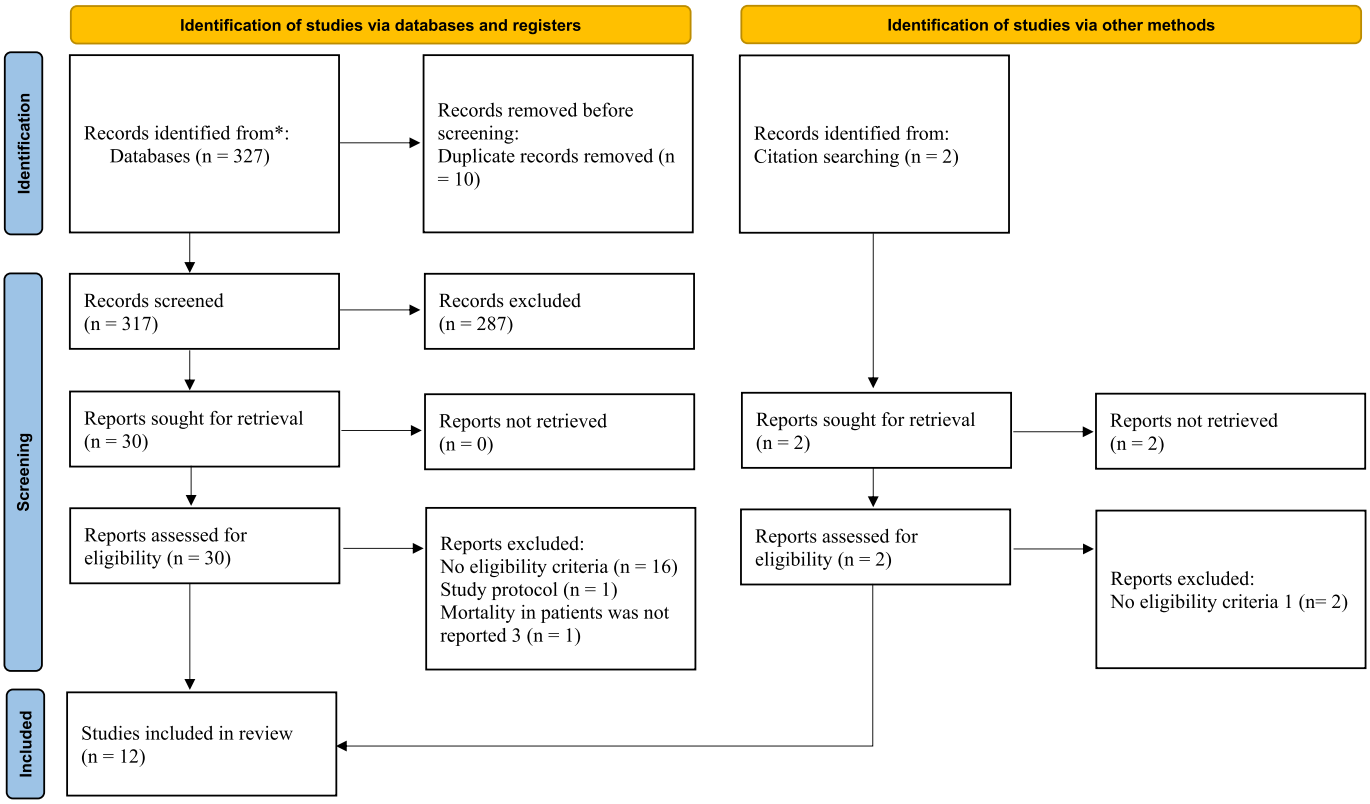

Fig. 1. A flow chart showing the stages of retrieving articles and assessing the eligibility criteria for network meta-analysis of treatments in patients hospitalized with COVID-19.
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

In a three arms RCT in Iran, that not connected to the network, patients randomized in three groups including Steroid + Azithromycin (n = 116), Azithromycin (n = 110), and Lopinavir/Ritonavir (n = 110). Based on the results of this RCT there was no significant difference among groups in term of death, admission to ISU and intubation. In the intention-to-treat analysis, the number of death in the above-mentioned groups were four, six, and six respectively, in addition, the number of patients who were admitted to intensive care units (ICU) were five, six, and seven respectively [28]. In another RCT that not connected to the network, high and low-dose dexamethasone were compared in patients with ARDS caused by COVID-19. The participants in this study were patients with SARS-Cov-2 pneumonia who develop acute respiratory distress syndrome, admitted in ICU. Based on the results of this study there was no differences between high and low-dose groups in term of mortality. The 28-day mortality rate in low dose and high dose groups was 39% and 41% respectively [29].

Discussion

In this NMA, the corticosteroids were compered simultaneously in patients with COVID-ARDS and COVID pneumonia. The treatments were ranked based on their effect on the risk of death. Based on the results if this NMA, methylprednisolone + UC was significantly effective than UC and received the first rank among eight treatments in the network. In addition, the risk of death among patients who received Methylprednisolone and Budesonide was lower than patients received only UC, however the effect sizes were not statistically significant.

In one of the included RCTs that conducted in Brazil, Methylprednisolone did not reduce mortality of hospitalized patients with COVID-19. Although, a lower mortality rate was found by a subgroup analysis in patients older than 60 years received MP. These patients were those who also presented a more pronounced systemic inflammatory status, as documented by high CRP values [13]. Through a per protocol analysis, but not a ITT analysis, conducted in Spain by L Corral-Gudino et al., MP administration was associated with a reduced risk of primary outcome [24].

There are some evidences in support of our finding about more efficacy of MP for COVID pneumonia and ARDS. It penetrates to lung acini better [31], and have a more concentration and persistent time in lung tissue with a slower elimination [32]. Also, prolonged MP use in ARDS could decrease both systemic inflammation and peripheral acquired glucocorticoid resistance by increasing glucocorticoid receptor activity and reducing in NF-κB DNA-binding [33]. In the study that used in silico method for identifying drug of COVID-19 it was shown that MP could improve outcomes in severe COVID-19 [34].

We had some limitations in our NMA. First, evaluation of the similarity as a main assumption for valid indirect estimates. Although we excluded one RCT because of violation of this assumption, however, this assumption may be violated. Necessarily, all effect modifiers that may affect the treatment effect, may not have been reported in the RCTs, and our assessment is based on the reported effect modifies, so this assumption may have been violated. Second, heterogeneity in usual care: in this study, we merged usual care, standard care, and placebo as usual care. The usual care as a common comparator in our NMA was not exactly the same across studies. Third, in this NMA we assessed only the mortality of patients, this is while, other such as treatment

Table 1
Characteristics of included RCTs available to compare corticosteroid drugs for survival in COVID-ARDS and COVID pneumonia.

Author	Country	Study population	Study Period (months)	Treatments	Primary outcomes	Sample size	Male (%)	Mean age	No. death
Dequin (2020)	France	Patients hospitalized with Intensive care unit (*ICU*)for COVID-19-related acute respiratory failure	1	T1: low-dose hydrocortisone (Hydrocortisone) T2: placebo (Placebo)	21-Day Mortality or Respiratory Support	T1: 76 T2: 73	T1: 69.2 T2: 68.5	T1: 63.1 T2: 66.3	T1: 32 T2: 37
Edalatifard (2020)	Iran	Patients hospitalized with Coronavirus Disease 2019	1	T1:standard care+ methylprednisolone (intravenous injection, 250 mg·day−1 for 3 days) (Methylprednisolone+ UC) T2: standard care(UC)	Recovery, Death	T1: 34 T2: 28	T1: 70.6 T2: 53.6	T1: 55.8 T2: 61.7	T1: 2 T2: 12
Horby (2021)	UK	Patients hospitalized with Coronavirus Disease 2019	1	T1: oral or intravenous dexamethasone (at a dose of 6 mg once daily) for 10 days+ usual care (Dexamethasone+ UC) T2: usual care(UC)	28-day mortality	T1: 2104 T2: 4321	T1: 63.6 T2: 63.6	T1: 66.9 T2: 65.8	T1: 482 T2: 1110
Jamaati (2021)	Iran	Patients hospitalized with mild to moderate acute respiratory distress syndrome (ARDS)due to Coronavirus Disease 2019	1	T1: Dexamethasone,20 mg/day from day 1–5 and then at 10 mg/day from day 6–10 + usual care (Dexamethasone+ UC) T2: usual care(UC)	Death, evaluate the clinical effects (Hospital stay days, ICU stay days, Noninvasive ventilation, Invasive mechanical ventilation, SOFA score)	T1: 25 T2: 25	T1: 72.0 T2: 76.0	T1: 58.5 T2: 64.25	T1: 16 T2: 15
Jeronimo (2021)	Brazil	Patients hospitalized with Coronavirus Disease 2019	1	T1: methylprednisolone (0.5 mg/kg) twice daily for 5 days (Methylprednisolone+UC) T2: placebo (Placebo)	28-day mortality	T1: 194 T2: 199	T1: 35.1 T2: 35.7	T1: 54 T2: 57	T1: 72 T2: 76
L Corral-Gudino (2021)	Spain	Patients hospitalized with receiving oxygen without mechanical ventilation, and with evidence of systemic inflammatory response	1	T1: methylprednisolone, (40 mg bid for 3 days followed by 20 mg bid for 3 days+ standard of care (Methylprednisolone+ UC) T2: standard of care (UC)	death, admission to the intensive care unit, or requirement for noninvasive ventilation	T1: 35 T2: 29	T1: 34.3 T2: 44.8	T1: 73 T2: 66	T1: 14 T2: 14
Ranjbar (2021)	Iran	Patients hospitalized with Coronavirus Disease 2019	1	T1: methylprednisolone (2 mg/kg/day) (Methylprednisolone+UC) T2: dexamethasone (6 mg/day) + usual care (Dexamethasone+ UC)	28-day mortality, clinical status	T1:44 T2: 42	T1: 38.6 T2: 47.6	T1: 56.2 T2: 61.3	T1: 8 T2: 15
Tomazini (2020)	Brazil	Patients hospitalized with COVID-19 and moderate to severe ARDS	1	T1: Twenty mg of dexamethasone intravenously daily for 5 days+ standard of care (Dexamethasone+ UC) T2: standard of care (UC)	ventilator-free days during the first 28 days, defined as being alive and free from mechanical ventilation	T1: 151 T2: 148	T1: 40.4 T2: 34.5	T1: 60.1 T2: 62.7	T1: 85 T2: 91
Angus (2020)	International	Adult patients with suspected or confirmed COVID-19 Admission to an intensive care unit (ICU)	1	T1: a fixed dose of intravenous hydrocortisone, 50 mg, every 6 h for 7 days T2: shock-dependent hydrocortisone, 50 mg, every 6 h T3: no hydrocortisone	respiratory and cardiovascular organ support–free days up to day 21, an ordinal end point with death within the hospital as the worst outcome	T1: 142 T2: 152 T3: 108	T1: 69.0 T2: 67.8 T3: 66.7	T1: 60.4 T2: 59.5 T3: 59.9	T1: 41 T2: 37 T3: 33
Ghanei (2021)	Iran	Hospitalized patients, 16 years of age or older	2	T1: hydroxychloroquine stat (400) + prednisolone [25] + Azithromycin (250) + naproxen (250) T2: hydroxychloroquine stat (400) + Azithromycin (250) + naproxen (250) T3: hydroxychloroquine stat (400) + Lopinavir/Ritonavir	The number of admissions to intensive care unit	T1: 120 T2: 116 T3: 116	T1: 47.5 T2: 47.4 T3: 52.5	T1: 58.2 T2: 57.6 T3: 58.4	T1: 4 T2: 6 T3: 6
Maskin (2022)	Argentina	Patients with COVID-19-Related Acute Respiratory Distress Syndrome	10	T1: Low-dose dexamethasone 8 mg T2: High-dose dexamethasone 16 mg	The ventilator-free days during the first 28 days, defined as the number of days alive and free from mechanical ventilation up to the	T1: 51 T2: 49	T1: 76.5 T2: 73.5	T1: 60.04 T2: 63.57	T1: 23 T2: 23

(*continued on next page*)

Table 1 (*continued*)

Author	Country	Study population	Study Period (months)	Treatments	Primary outcomes	Sample size	Male (%)	Mean age	No. death
Yu (2021)	UK	People aged at least 65 years, or at least 50 years with comorbidities, and had ongoing symptoms from PCR-confirmed or suspected COVID-19	12	T1: Inhaled budesonide T2: Usual care	28th day from randomization. COVID-19-related hospital admission or death within 28 days	T1: 990 T2: 1858	T1: 40.8 T2: 29.1	T1: 64.7 T2: 63.8	T1: 6 T2: 10

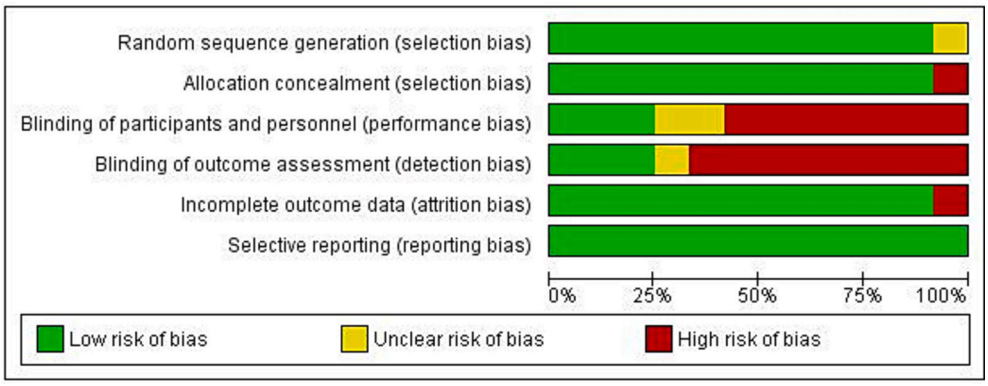

Fig. 2. Summary results of risk of bias assessment.

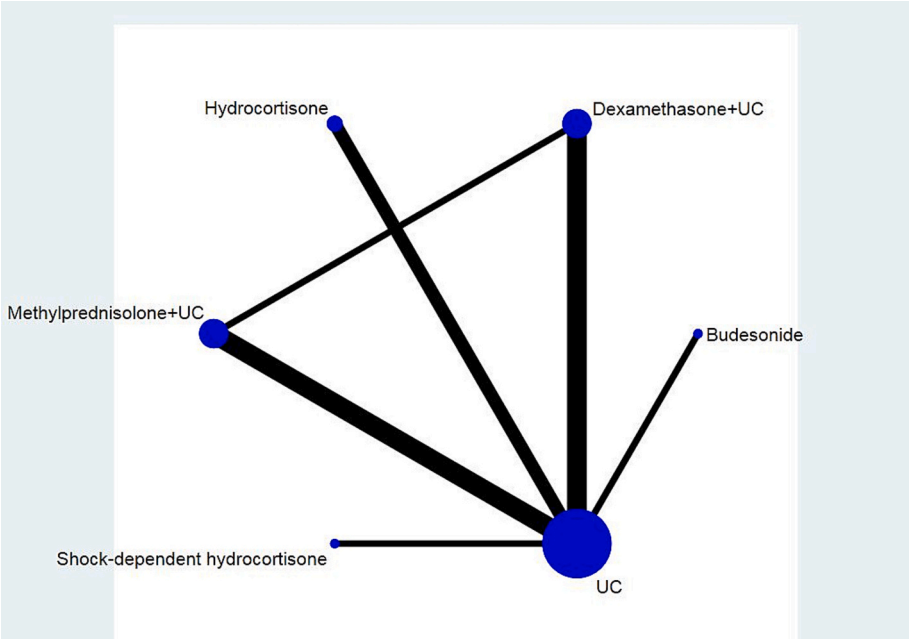

Fig. 3. Network of treatments in patients hospitalized with COVID-19.

complications, length of hospitalization, or time-to-discharge are also important outcomes. Fourth, the power of our network for estimating the indirect effect sizes may be affected by the low sample size of some RCTs included which also leading wide confidence intervals for some indirect effects size [35]. Thus the sparse-data bias may be present in our results [36]. Fifth, because of the low number of included RCTs in the network, we could not evaluate the publication bias in this NMA [37].

We compared simultaneously corticosteroid drugs for patients with COVID-19 in a review, Nevertheless, the information may be helpful in highlighting gaps in clinical knowledge regarding a better understanding of corticosteroid drugs' efficacy and effectiveness in patients with COVID-ARDS and COVID pneumonia.

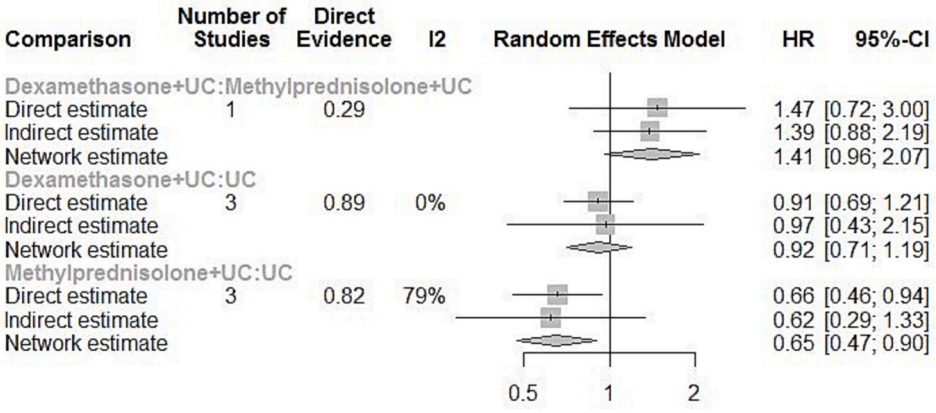

Fig. 4. Forest plot for results of consistency assumption using loop specific approach in the network of treatments.

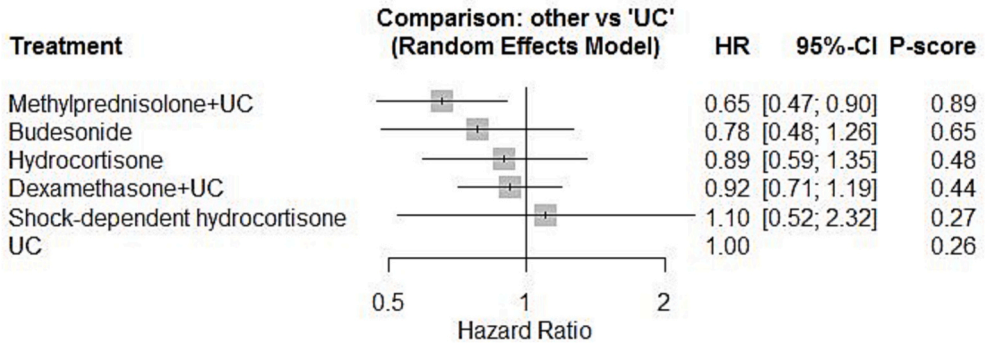

Fig. 5. Forest plot for comparison of all treatments in network with UC and related P-score for ranking of the treatments.

Table 2
League table for simultaneous comparison of all treatments in the network.

Methylprednisolone+UC	.	.	0.68 (0.33, 1.39)	.	0.66 (0.46, 0.94)
0.83 (0.47, 1.49)	Budesonide	.	.	.	0.78 (0.48, 1.26)
0.73 (0.43, 1.23)	0.87 (0.46, 1.65)	Hydrocortisone	.	.	0.89 (0.59, 1.35)
0.71 (0.48, 1.04)	0.85 (0.49, 1.47)	0.97 (0.60, 1.59)	Dexamethasone+UC	.	0.91 (0.69, 1.21)
0.59 (0.26, 1.34)	0.71 (0.29, 1.73)	0.81 (0.35, 1.91)	0.83 (0.38, 1.85)	Shock-dependent hydrocortisone	1.10 (0.52, 2.32)
0.65 (0.47, 0.90)	0.78 (0.48, 1.26)	0.89 (0.59, 1.35)	0.92 (0.71, 1.19)	1.10 (0.52, 2.32)	UC

Conclusion

Results of this NMA indicated that Methylprednisolone + UC seems to be a better treatment for patients with COVID-ARDS and COVID pneumonia.

Author contributions

Literature search: MM, ADI, Data collection: MM, ADI, Study design: ADI, MAM, Analysis of data: ADI, MM, MN, Manuscript preparation: MM, ADI, MAM, MN, ShA, RA, Review of manuscript: MM, ADI, MAM, MN, ShA, RA.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data for this study is available at the manuscript.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gloepi.2023.100116.

References

[1] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42.

[2] Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. Jama. 2020;324(13):1307–16.

[3] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med 2020;383(19):1813–36.

[4] Dequin P-F, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. JAMA. 2020;324(13):1298–306.

[5] Guillon A, Hiemstra P, Si-Tahar M. Pulmonary immune responses against SARS-CoV-2 infection: harmful or not? Intensive Care Med 2020;46(10):1897–900.

[6] Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473–4.

[7] Sinha P, Matthay M, Calfee C. Is a "cytokine storm" relevant to COVID-19? JAMA Intern Med 2020;180(9):1152–4.

[8] Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, 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.

[9] Wang X, Du Z, Huang G, Pasco RF, Fox SJ, Galvani AP, et al. Effects of cocooning on coronavirus disease rates after relaxing social distancing. Emerg Infect Dis 2020;26(12):3066–8.

[10] Singanayagam A, Glanville N, Girkin JL, Ching YM, Marcellini A, Porter JD, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. Nat Commun 2018;9(1):2229.

[11] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2020;384(8):693–704.

[12] Group TRC. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med 2020;384(8):693–704.

[13] Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2021;72(9). e373-e81.

[14] Doosti-Irani A, Nazemipour M, Mansournia MA. What are network meta-analyses (NMAs)? A primer with four tips for clinicians who read NMAs and who perform them (methods matter series). Br J Sports Med 2020;55:520–1.

[15] Leucht S, Chaimani A, Cipriani AS, Davis JM, Furukawa TA, Salanti G. Network meta-analyses should be the highest level of evidence in treatment guidelines. Eur Arch Psychiatry Clin Neurosci 2016;266(6):477–80.

[16] Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: Cochrane handbook for systematic reviews of interventions; 2019. p. 205–28.

[17] Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013;42(1):332–45.

[18] Mansournia MA, Collins GS, Nielsen RO. A CHecklist for statistical assessment of medical papers (the CHAMP statement): explanation and elaboration. Br J Sports Med 2021;55(18):1009–17.

[19] Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PloS One 2013;8(10):e76654.

[20] Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, et al. Netmeta: an R package for network meta-analysis using frequentist methods. J Stat Softw 2023;106(2):1–40.

[21] Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15:58.

[22] Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J 2020;56(6).

[23] Jamaati H, Hashemian SM, Farzanegan B, Malekmohammad M, Tabarsi P, Marjani M, et al. No clinical benefit of high dose corticosteroid administration in patients with COVID-19: a preliminary report of a randomized clinical trial. Eur J Pharmacol 2021;897:173947.

[24] Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia : an open-label randomized trial (GLUCOCOVID). Wien Klin Wochenschr 2021;133(7–8):303–11 (3).

[25] Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infect Dis 2021;21(1):337.

[26] Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020;324(13):1307–16.

[27] Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, 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.

[28] Ghanei M, Solaymani-Dodaran M, Qazvini A, Ghazale AH, Setarehdan SA, Saadat SH, et al. The efficacy of corticosteroids therapy in patients with moderate to severe SARS-CoV-2 infection: a multicenter, randomized, open-label trial. Respir Res 2021;22(1):245.

[29] Maskin LP. High- versus low-dose dexamethasone for the treatment of COVID-19-related acute respiratory distress syndrome: a multicenter, randomized open-label clinical trial. J Intensive Care Med 2022;37(4):491–9.

[30] Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet (London, England) 2021;398(10303):843–55.

[31] Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. Lancet (London, England) 1983;2(8357):995–7.

[32] Greos LS, Vichyanond P, Bloedow DC, Irvin CG, Larsen GL, Szefler SJ, et al. Methylprednisolone achieves greater concentrations in the lung than prednisolone. A pharmacokinetic analysis. Am Rev Respir Dis 1991;144(3 Pt 1):586–92.

[33] Meduri GU, Siemieniuk RAC, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. J Intensive Care 2018;6:53.

[34] Draghici S, Nguyen TM, Sonna LA, Ziraldo C, Vanciu R, Fadel R, et al. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. Bioinformatics (Oxford, England) 2021:btab163.

[35] Mills EJ, Ghement I, O'Regan C, Thorlund K. Estimating the power of indirect comparisons: a simulation study. PloS One 2011;6(1):e16237.

[36] Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. BMJ (Clin Res Ed) 2016;352:i1981.

[37] Trinquart L, Chatellier G, Ravaud P. Adjustment for reporting bias in network meta-analysis of antidepressant trials. BMC Med Res Methodol 2012;12:150.

[38] Mansournia MA, Higgins JP, Sterne JA, Hernán MA. Biases in randomized trials: a conversation between trialists and epidemiologists. Epidemiology 2017;28(1):54.

[39] Greenland S, Mansournia MA, Joffe M. To curb research misreporting, replace significance and confidence by compatibility: a preventive medicine golden jubilee article. Preventive Medicine 2022:107127.

[40] Mansournia MA, Nazemipour M, Etminan M. P-value, compatibility, and S-value. Global Epidemiology 2022;4:100085.

[41] Mansournia MA, Collins GS, Nielsen RO, Nazemipour M, Jewell NP, Altman DG, et al. CHecklist for statistical Assessment of Medical Papers: the CHAMP statement. Br J Sports Med 2021;55(18):1002–3.