






Efficacy of pharmacological interventions in COVID-19: A network meta-analysis

Sandhiya Selvarajan¹  | Annuja Anandaradje¹  | Santhosh Shivabasappa¹  |
Deepthy Melepurakkal Sadanandan²  | N. Sreekumaran Nair²  | Melvin George³ 

¹Department of Clinical Pharmacology, JIPMER, Puducherry, India

²Department of Biostatistics, JIPMER, Puducherry, India

³Department of Clinical Pharmacology, SRM Medical College Hospital & Research Centre, SRMIST, Chennai, Tamil Nadu, India

Correspondence

Sandhiya Selvarajan, Additional professor and Head, Department of Clinical Pharmacology, JIPMER, Puducherry India.

Email: sandhiyaselvarajan@gmail.com

Aims: To perform network meta-analysis for a head-to-head comparison of various interventions used in coronavirus disease 2019 (COVID-19) on mortality, clinical recovery, time to clinical improvement and the occurrence of serious adverse events.

Methods: Systematic search was performed using online databases with suitable MeSH terms including coronavirus, COVID-19, randomized controlled trial, hydroxychloroquine, lopinavir/ritonavir, tocilizumab, remdesivir, favipiravir, dexamethasone and interferon- β . Data were independently extracted by 2 study investigators and analysed.

Results: Out of 1225 studies screened, 23 were included for qualitative and quantitative analysis. Among the drugs studied, dexamethasone reduces mortality by 10%, with a relative risk of 0.90 (95% confidence interval [0.82–0.97]) and increases clinical recovery by 6% (relative risk 1.06, 95% confidence interval [1.02–1.10]) compared to standard of care. Similarly, remdesivir administered for 10 days increased clinical recovery by 10%, reduced time to clinical improvement by 4 days and lowered the occurrence of serious adverse events by 27% as compared to standard of care.

Conclusion: In comparison to standard of care, dexamethasone was found to increase clinical recovery and lower mortality; remdesivir was significantly associated with a lower risk of mortality as compared to tocilizumab and higher clinical recovery and shorter time to clinical improvement as compared to hydroxychloroquine and tocilizumab; remdesivir followed by tocilizumab were found to have lesser occurrence of serious adverse events in patients with moderate to severe COVID-19.

KEYWORDS

clinical recovery, dexamethasone, hydroxychloroquine, mortality, remdesivir

1 | BACKGROUND

Coronavirus disease 2019 (COVID-19) has undisputedly become 1 of the greatest medical crises to ravage humanity in the last decade. Nearly 209 million people have been diagnosed with COVID-19 to date and as many as 4.4 million have succumbed to the disease.¹ While patients with the mild disease recover with supportive treatment, the management of patients with moderate and

severe forms of COVID-19 continues to be a daunting challenge. Several measures have been attempted to improve the clinical recovery rate, reduce viral replication, suppress the exaggerated immune response and reduce mortality. The pharmacological options that have been evaluated in clinical trials with COVID-19 include corticosteroids, tocilizumab, hydroxychloroquine (HCQ), antiviral agents such as remdesivir, a combination of lopinavir and ritonavir, and favipiravir.

In the earlier days of pandemic, HCQ, an antimalarial drug used widely in rheumatoid arthritis was proposed to be useful on the basis of *in vitro* evidence.² Nevertheless there have been conflicting reports about the effectiveness of HCQ with earlier reports favouring the utility of this medication in treating COVID-19.³ Subsequently remdesivir was approved by the US Food and Drug Administration (FDA) for the treatment of severe COVID-19 infection on the basis of an improvement in the time to recovery following hospitalization.⁴ However the drug was not found to be effective in reducing mortality as per the results of the World Health Organization (WHO) Solidarity trial.⁵ Although corticosteroids interfere with the body's ability to control viral replication, few studies have highlighted their benefits in reducing mortality in severe COVID-19 patients admitted in the intensive care unit.⁶ Additionally, tocilizumab, an interleukin-6 receptor antagonist has been shown to reduce the need for mechanical ventilation in patients with severe COVID-19, although few studies have shown its inadequate efficacy in preventing intubation or death in moderately ill hospitalized patients with COVID-19.^{7,8} Similarly, the use of other repurposed drugs such as interferon, favipiravir and a combination of lopinavir and ritonavir have shown conflicting results in COVID-19. Although many drugs have been claimed to have potential benefit in COVID-19, there are few network meta-analyses (NMAs) comparing the effect of these agents on mortality and clinical recovery. Hence, we aimed to perform an NMA with a head-to-head comparison of various interventions used in COVID-19 to assess their outcome on mortality, clinical recovery, time to clinical improvement and serious adverse events (SAEs).

2 | METHODS

This systematic review and NMA was carried out in accordance with the registered protocol in PROSPERO (CRD42021246551) and abides by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension statement for reporting the systematic reviews incorporating NMA of health care interventions.

2.1 | Identification of studies

The electronic bibliographic databases namely Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Cochrane Methodology Register), PubMed and PubMed Central were searched from December 2020 to February 2021. The search/MeSH terms applied were coronavirus, COVID-19, randomized controlled trial, hydroxychloroquine, lopinavir/ritonavir, tocilizumab, remdesivir, favipiravir, dexamethasone and interferon- β .

2.2 | Selection criteria

All the randomized controlled studies in hospitalized COVID-19 patients of all age groups and sex with any pharmacological

What is already known about this subject

- Globally, various newer molecules and existing drugs have been evaluated as potential treatments for coronavirus disease 2019 (COVID-19).
- The earlier meta-analyses compared the various interventions in a heterogeneous population of COVID-19 with a major focus on all-cause mortality.
- There were inadequate data on the efficacy of drugs on recovery from randomized controlled trials in a homogeneous population of COVID-19 cases.

What this study adds

- This network meta-analysis provides evidence towards head-to-head comparison of various interventions on outcomes such as mortality, clinical recovery, time to clinical improvement and occurrence of serious adverse events in a homogeneous population of COVID-19 patients.
- This study reinforces the effect of dexamethasone on reducing mortality in hospitalized patients with moderate to severe COVID-19. Dexamethasone was also found to improve clinical recovery.
- There is evidence towards improved clinical recovery, reduced time to clinical improvement and lesser occurrence of serious adverse events following administration of remdesivir in patients with moderate to severe COVID-19.

treatments were included. The exclusion criteria were studies done for prevention of COVID-19 in healthy populations, abstract-only articles, case reports, conference presentations, editorials, reviews, expert opinions, articles in a language other than English, etc.

2.3 | Outcomes

The outcomes assessed from the included studies were mortality, clinical recovery, time to clinical improvement and the occurrence of SAEs. For assessing the outcomes of mortality and clinical recovery, studies reporting death due to any cause by day 28 and discharge from the hospital by day 28 of admission were considered. Time to clinical improvement has been defined as time to discharge or time to reduction in disease severity to a state of no requirement of supplemental oxygen whichever occurred earlier. The same definitions were

used to extract the data from the included studies. Safety was assessed based on the occurrence of SAEs among the participants of the included studies.

2.4 | Study selection and data extraction

Titles and/or abstracts of studies were retrieved using the search strategy as mentioned. A standardized, pre-formatted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. The data extracted include study setting, study population, study type, participant demographics and baseline characteristics, details of the intervention and control conditions, study methodology, randomization details, mortality, clinical recovery, time to clinical improvement, and the occurrence of SAEs. All the data were extracted either from text, tables, or figures of the published articles. Data from the figures and graphs were extracted using WebPlotDigitizer software (version 4.1, <https://automeris.io/WebPlotDigitizer/>). Two of the review authors extracted the data independently, identified discrepancies and resolved them through discussion with a third author.

2.5 | Risk of bias

The NMA includes only randomised controlled trials in which the risk of bias was assessed according to the standards laid down by the Cochrane handbook of meta-analysis.⁹ The domains of bias assessment include: randomization sequence generation, treatment allocation concealment, blinding, completeness of outcome data, selective reporting and other possible sources of bias. Disagreements between the review authors over the risk of bias in particular studies were resolved by discussion, with the involvement of a third review author, whenever necessary.

2.6 | Statistical analysis

An NMA within a frequentist framework was carried out using *netmeta* package available in R software version 4.1.1.¹⁰ In a frequentist approach, the *netmeta* package uses graph theory techniques to describe the relative treatment effects of several treatments.¹¹ Network plots were drawn for visualizing the network geometry of the available evidence using STATA version 15.1 (Stata Corp, TX, USA).¹² Both global and local inconsistencies were assessed. Node splitting was done to check for the local inconsistency.¹³ The statistical heterogeneity was quantified and tested using the I^2 and generalized Cochrane Q statistic. A random-effect model was used if sufficient heterogeneity was detected ($I^2 > 50\%$), otherwise a fixed effect model was used.

Summary estimates were reported as relative risk (RR) along with 95% confidence interval (CI) for dichotomous outcomes like mortality, clinical recovery and SAEs whereas difference in means (MD) and

corresponding 95% CI for the continuous outcome (time to clinical improvement). A P -value $< .05$ was considered statistically significant. Net-league plots were used to represent all pairwise summary estimates from NMA. Reference-based Forest plots were plotted to display the pooled effect estimates obtained from the comparisons of different treatments to the standard of care. The standard of care was considered as the reference.

P-score, a frequentist equivalent of the surface under the cumulative ranking (SUCRA) value was estimated in order to rank the treatments.¹⁴ P-score (range from 0 to 1) represents the mean extent of certainty that a treatment is superior to other treatments, averaged over all competing treatments. Treatment with the highest P-score (near to 1) was considered as superior when compared to other competing treatments. Comparison-adjusted funnel plots were constructed to assess the publication bias and the asymmetry of the funnel was tested using Egger's test.¹⁵

A sensitivity analysis was carried out to assess the robustness of the findings by excluding those studies with a mild-moderate population. The relative treatment estimates were obtained for those studies comprising of only moderate to severe population and the results were compared with the overall analysis.

3 | RESULTS

3.1 | Study selection and characteristics

After screening 1225 titles and abstracts, 23 randomized controlled trials (RCTs) met the eligibility criteria and were included in the NMA (Figure 1). A total of 31 226 hospitalized patients with moderate to severe COVID-19 in the included RCTs were assessed. The median age of the participants ranged from 40 to 69 years with 37.5% being women. The study design and characteristics of the trials included in the analysis are as enumerated in (Table 1).^{5,6,16–36} Of the 23 studies included, 6 were double-blinded (23%) and the rest were open-label (77%). Most trials had reported outcomes at 28–30 days except for 3 studies that had reported outcomes at 14 days.

3.2 | NMA

Seven different interventions namely dexamethasone, remdesivir, tocilizumab, HCQ, combination of lopinavir/ritonavir, favipiravir and interferon- β were evaluated in this NMA. A fixed-effect model was selected for analysing the data for mortality, clinical recovery and SAEs ($I^2 = 0\%$ [95% CI 0–50.0]; $Q = 14.15$, $P = .66$, $I^2 = 35\%$ [95% CI 0–71.2]; $Q = 10.77$, $P = 0.15$, $I^2 = 41.7\%$ [95% CI 0–70.4]; $Q = 18.86$, $P = 0.06$ respectively) as there was no overall heterogeneity. A random-effect model was selected for reporting data on time to clinical improvement, since there was high heterogeneity found across the studies ($I^2 = 85.9\%$ [95% CI 65.5–94.3]; $Q = 21.31$, $P < .001$). Both global and local inconsistencies were assessed and no statistical inconsistency was detected across the studies.

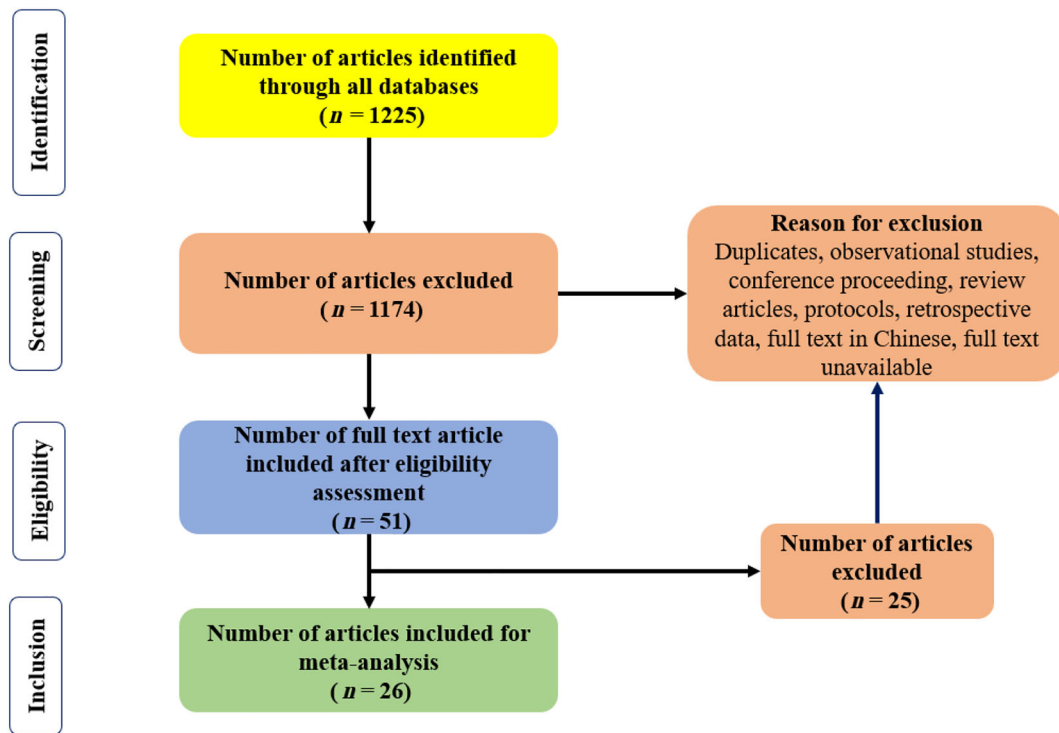


FIGURE 1 PRISMA flowchart delineating the study selection for network meta-analysis

3.3 | Network plot

Network plots depicting the interventions have been drawn for each of the outcomes with the standard of care as the most common comparator (Figure 2). Two of the included trials had evaluated treatment against active comparator i.e. remdesivir administered for 10 days (R10) with remdesivir administered for 5 days (R5). Hence, we have classified remdesivir administered for 10 days (R10) as a different treatment node from remdesivir administered for 5 days (R5). No statistical incoherence was detected with this approach.

3.4 | Mortality

All the included trials reported mortality, and the network analysis involved 8 treatments and 12 comparisons. The analysis suggested a reduction in mortality of hospitalized patients with dexamethasone (RR 0.90, 95% CI [0.82–0.97]) compared to the standard of care alone (Figure 3A). However, other treatment interventions did not show any significant effect on mortality when compared with standard of care.

3.5 | Clinical recovery

Among the included studies, 14 RCTs had analysed clinical recovery. Remdesivir administered for 10 days has shown 10% higher clinical recovery when compared to standard of care (RR 1.10, 95% CI [1.04–1.15]). This was followed by dexamethasone with an increased clinical

recovery by 6% compared to standard of care (RR 1.06, 95% CI [1.02–1.10]; Figure 3B). The remaining treatment interventions showed no significant effect on clinical recovery compared to standard of care.

3.6 | Time to clinical improvement

Time for clinical improvement was reported in only 11 of the 23 studies. Remdesivir given for 10 days and 5 days shortened the time to recovery when compared to the standard of care (MD: -4.08 d, 95% CI [-5.47 to -2.68 d] and MD: -3.98 d, 95% CI [-6.23 to -1.73 d], respectively; Figure 3C). None of the other interventions had any significant effect on the time to recovery.

3.7 | SAEs

Only 16 of the included trials had reported on the occurrence of SAEs. Remdesivir administered for 10 days was found to be associated with a lower occurrence of SAEs compared to standard care (RR-0.73, 95% CI [0.61–.87]) followed by tocilizumab (RR-0.76, 95% CI [0.64–0.91]; Figure 3D).

3.8 | Net league table

Net league table (Tables 2A–D) with relative treatment effect estimates and their 95% CIs for all possible treatment combinations shows

TABLE 1 Baseline characteristics of the included studies

Author (n)	Intervention (n)	Age (y) [#]	Female, n (%)	Mortality, n (%)	Clinical recovery, n (%)	SAE, n (%)
Tomazini et al. (299)	Dexamethasone (151)	60.1 (15.8)	61 (40.4)	85 (56.3)	42 (27.8)	5 (3.3)
	Standard care (n = 148)	62.7 (13.1)	51 (34.5)	91 (61.5)	25 (16.9)	9 (6.1)
Horby et al. (6425)	Dexamethasone (n = 2104)	66.9 (15.4)	766 (36)	482 (22.9)	1416 (67.3)	4
	Standard care (n = 4321)	65.8 (15.8)	1572 (36)	1110 (25.7)	2748 (63.6)	-
Biegel et al.* (1062)	Remdesvir (n = 541)	58.6 (14.6)	189 (34.9)	59 (10.9) [§]	399 (73.7)	131 (24.6)
	Standard care (n = 521)	59.2 (15.4)	189 (36.3)	77 (14.7) [§]	352 (57.5)	163 (31.6)
Goldman et al. (397)	Remdesvir for 5 days (n = 200)	61 (50–69)	80 (40)	16 (8) [§]	120 (60) [§]	42 (21)
	Remdesvir for 10 days (n = 197)	62 (50–71)	63 (32)	21 (11) [§]	103 (52.3)	68 (35)
Wang et al.* (236)	Remdesvir (n = 158)	66 (57–73)	69 (44)	22 (14)	92 (61.3)	28 (18)
	Standard care (n = 78)	64.0 (53–70)	27 (35)	10 (13)	45 (58)	20 (26)
Spinner et al. (594)	Remdesvir for 10 days (n = 193)	56 (45–66)	75 (39)	3 (2)	174 (90)	10 (5)
	Remdesvir for 5 days (n = 191)	58 (48–66)	77 (40)	2 (1)	170 (89)	9 (5)
	Standard care (n = 200)	57 (45–66)	75 (38)	4 (2)	166 (83)	18 (9)
Solidarity Trial - Remdesvir (5451)	Remdesvir (n = 2743)	-	1037 (37.8)	301 (12.5)	-	-
	Standard care (n = 2708)	-	983 (36.3)	303 (12.7)	-	-
Hermine et al. (130)	Tocilizumab (n = 63)	64 (57.1–74.3)	19 (30)	7 (11)	52 (83)	20 (32)
	Standard care (n = 67)	63.3 (57.1–72.3)	23 (34)	8 (12)	49 (73)	29 (43)
Salvarani et al. (126)	Tocilizumab (n = 60)	61.5 (51.5–73.5)	20 (33.3)	2 (3.3)	54 (90)	-
	Standard care (n = 66)	60.0 (54.0–69.0)	29 (43.9)	1 (1.6)	58 (92.1)	-
Stone et al.* (243)	Tocilizumab (n = 161)	61.6 (46.4–69.7)	65 (40)	9 (5.6)	147 (91.3)	36 (22.3)
	Standard care (n = 82)	56.5 (44.7–67.8)	37 (45)	3 (3.8)	72 (88.9)	38 (46.3)
Rosas et al.* (438)	Tocilizumab (n = 294)	60.9 (14.6)	89 (30.3)	58 (19.7)	-	102 (34.6)
	Standard care (n = 144)	60.6 (13.7)	43 (29.9)	28 (19.4)	-	55 (38.1)
Salama et al.* (377)	Tocilizumab (n = 249)	56.0 (14.3)	99 (39.8)	26 (10.4)	-	38 (15.2)
	Standard care (n = 128)	55.6 (14.9)	55 (43)	11 (8.5)	-	25 (19.5)
Veiga et al. (129)	Tocilizumab (n = 65)	57.4 (15.7)	21 (32)	14 (21)	34 (52)	11 (16)
	Standard care (n = 64)	57.5 (13.5)	22 (31)	6 (9)	32 (50)	7 (11)
Ulrich et al.* (128)	HCQ (n = 67)	66.5 (16.4)	22 (32.8)	13 (19.4)	-	-
	Standard care (n = 61)	65.8 (16.0)	30 (49.2)	6 (9.8)	-	-
Tang et al. (150)	HCQ (n = 75)	48 (14.1)	33 (44)	-	33 (59.9)	2 (3)
	Standard care (n = 75)	44.1 (15)	35 (47)	-	43 (66.6)	0
Lyngbakken et al. (53)	HCQ (n = 27)	56 (41–72)	8 (29.6)	1 (3.8)	-	5 (18.5)
	Standard care (n = 26)	69 (51–74)	10 (38.5)	1 (4)	-	6 (23.1)
Solidarity Trial - HCQ (1853)	Hydroxychloroquine (n = 947)	-	373 (39.4)	104 (10.2)	-	-
	Standard care (n = 906)	-	371 (40.9)	84 (8.9)	-	-
Abd-Elsalam et al. (194)	Hydroxychloroquine (n = 97)	40.35 (18.65)	41 (42.3)	6 (6.1)	-	-
	Standard care (n = 97)	41.09 (20.07)	39 (40.2)	5 (5.1)	-	-
Cavalcanti et al. (665)	Hydroxychloroquine (n = 221)	51.3 (14.5)	79 (35.7)	1 (3)	-	2 (1)
	Standard care (n = 227)	49.9 (15.90)	104 (45.81)	1 (3)	-	2 (1.1)
Yan Lou et al. (19)	Favipiravir (n = 9)	58 (8.1)	2 (22.2)	-	5 (55)	-
	Standard care (n = 10)	46.6 (14.1)	2 (20)	-	5 (50)	-
Recovery group (5040)	Lopinavir + ritonavir (n = 1616)	66 (16)	643 (40)	374 (23)	-	1 (0.06)
	Standard care (n = 3424)	66.4 (15.8)	1320 (39)	767 (22)	-	-
Solidarity Trial (2771)	Lopinavir + Ritonavir (n = 1399)	-	548 (39.1)	148 (9.7)	-	-
	Standard care (n = 1372)	-	570 (41.5)	146 (10.3)	-	-

(Continues)

TABLE 1 (Continued)

Author (n)	Intervention (n)	Age (y) [#]	Female, n (%)	Mortality, n (%)	Clinical recovery, n (%)	SAE, n (%)
Cao et al. (199)	Lopinavir + ritonavir (n = 99)	58 (50–68)	37 (38)	19 (19.2)	-	19 (20)
	Standard care (n = 100)	58 (48–68)	41 (41)	25 (25)	-	32 (32.3)
Davoudi-Monfared (81)	Interferon β 1a (n = 42)	56.5 (47.25–67.25)	20 (47.61)	8 (19.4)	-	-
	Standard care (n = 39)	61 (50–70)	17 (43.58)	15 (38.46)	-	-
Rahmani (66)	Interferon β 1b (n = 33)	60 (47–73)	13 (39.39)	2 (6.06)	-	-
	Standard care (n = 33)	61 (50–71)	14 (42.42)	6 (18.18)	-	-
Solidarity Trial (4100)	Interferon β 1a (n = 2050)	-	747 (36.4)	243 (12.9)	-	-
	Standard care (n = 2050)	-	772 (37.6)	216 (11)	-	-

*Double blind placebo controlled,

[#]Mean (standard deviation) or median (interquartile range),

[§]Assessed at 14 days,

SAE, serious adverse events; -, values not available.

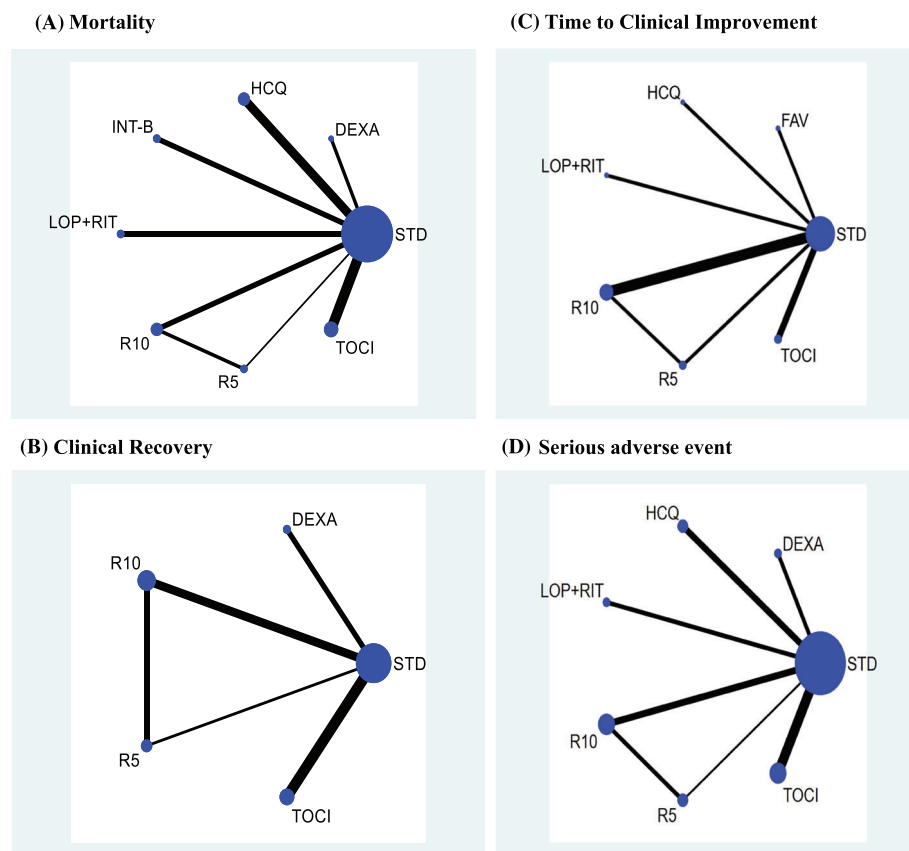


FIGURE 2 Network plot depicting network geometry of all treatments

that dexamethasone and remdesivir were significantly associated with a lower risk of mortality as compared to HCQ. In addition, remdesivir was significantly associated with a lower risk of mortality as compared to tocilizumab and higher clinical recovery and shorter time to clinical improvement as compared to HCQ and tocilizumab. Remdesivir and tocilizumab were associated with a lower occurrence of SAEs as compared to standard of care.

Sensitivity analysis with studies involving only moderate to severe cases, found that dexamethasone and remdesivir were

significantly associated with lower risk of mortality as compared to standard of care and HCQ respectively (Table S2A). Similarly in sensitivity analysis dexamethasone and remdesivir were found to be significantly associated with improved clinical recovery as compared to standard of care (Table S2B). In addition, sensitivity analysis findings were similar to the overall analysis of remdesivir having a shorter duration for clinical improvement as compared to tocilizumab and with a lower occurrence of SAEs as compared to standard of care (Table S2C, D).

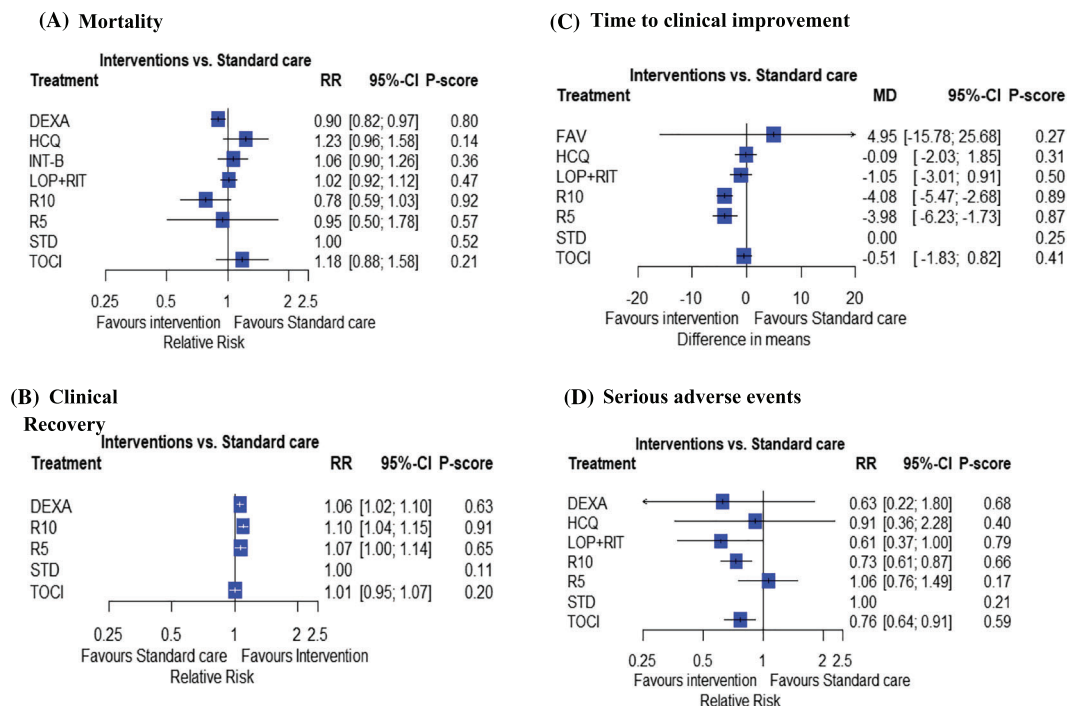


FIGURE 3 Forest plot comparing single treatment to standard of care for various outcomes. CI, confidence interval; RR, risk ratio

3.9 | P-score

The P-score can be interpreted as the mean extent of certainty that a treatment is better than other treatments, averaged over all competing treatments. Remdesivir administered for 10 days followed by dexamethasone were found to have a higher probability of reducing mortality as compared to other treatments (Table 3). Also, remdesivir given for 10 days was found to have a higher probability on improving clinical recovery as compared to other competing treatments included in the study. However, lopinavir/ritonavir combination had a 79% certainty of being ranked first with fewer SAEs, followed by dexamethasone and remdesivir given for 10 days.

3.10 | Risk of bias in the included studies

Risk of bias in the included studies as assessed by Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0) is presented in Figure S1. Overall, the risk of bias was rated as low in 7 RCTs, some concerns in 9 and high in the remaining RCTs.

3.11 | Publication bias

Comparison of adjusted funnel plots were made for the visual assessment of asymmetry (Figure 4). The publication bias as assessed through Egger's test was found to be nonsignificant for mortality, clinical recovery, time to clinical improvement and SAEs ($P = .50$, $P = .69$, $P = .13$ and $P = .44$, respectively). However, due to fewer studies

reporting clinical recovery and time for clinical improvement, there is a possibility that the power of the test could be low enough to distinguish chance and real asymmetry in such cases.

4 | DISCUSSION

The present NMA was done to generate evidence towards the various drugs evaluated in the treatment of moderate to severe hospitalized COVID-19 patients. Our meta-analysis has found that dexamethasone reduces mortality by 10%, with a RR of 0.90 (95% CI [0.82–0.97]) compared to the standard of care. The findings are consistent with the results of NMA by Kim *et al.* and Siemieniuk *et al.*^{37,38} The NMA by Kim *et al.* based on 40 RCTs and 70 observational studies has concluded that the risk of mortality was significantly reduced with corticosteroids (odds ratio, OR [95% CI] 0.78 [0.66–0.91], $P = .002$) compared to standard care in moderate to severe COVID-19 patients. They have also concluded that the odds OR for the association between corticosteroids and mortality were similar for dexamethasone and hydrocortisone.³⁷ Similarly the living NMA by Siemieniuk *et al.*, based on 41 trials found that glucocorticoids probably reduce mortality in patients with severe COVID-19 (OR [95% CI] 0.87 [0.77–0.98]).³⁸ Likewise, a meta-analysis by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working group reported that administration of dexamethasone in critically ill hospitalized COVID-19 patients had an odd's ratio of 0.64 (95% CI, 0.50–0.82; $P < .001$) for mortality compared to standard care.³⁹ Further the RECOVERY trial had found that the incidence of death was lower in the dexamethasone group (29.3%) than that in the standard care

TABLE 2 Net league table of all pairwise comparisons in network meta-analysis

A. Mortality							
DEXA							
*0.73 (0.56–0.95)	HCQ						
0.84 (0.70–1.02)	1.16 (0.85–1.57)	INT					
0.88 (0.78–1.00)	1.21 (0.92–1.59)	1.05 (0.86–1.27)	LOP+RIT				
1.15 (0.86–1.54)	1.58 (1.08–2.30)*	1.36 (0.98–1.89)	1.30 (0.97–1.75)	R10			
0.95 (0.50–1.79)	1.30 (0.66–2.57)	1.12 (0.58–2.16)	1.07 (0.57–2.03)	0.82 (0.46–1.47)	R5		
0.90 (0.82–0.97)*	1.23 (0.96–1.58)	1.06 (0.90–1.26)	1.02 (0.92–1.12)	0.78 (0.59–1.03)	0.95 (0.50–1.78)	STD	
0.76 (0.56–1.03)	1.04 (0.71–1.54)	0.90 (0.64–1.27)	0.86 (0.63–1.18)	0.66 (0.44–0.99)*	0.80 (0.40–1.61)	0.85 (0.63–1.14)	TOCI
B. Clinical recovery							
DEXA							
0.97 (0.91–1.03)	R10						
1.00 (0.92–1.07)	1.03 (0.97–1.08)			R5			
1.06 (1.02–1.10)	1.10 (1.04–1.15)*			1.07 (1.00–1.14)		STD	
1.05 (0.98–1.13)	1.09 (1.00–1.18)		1.06 (0.97–1.16)		0.99 (0.93–1.06)		TOCI
C. Time to clinical improvement							
FAV							
5.04 (–15.78–25.86)	HCQ						
6.00 (–14.82–26.82)	0.96 (–1.80–3.72)	LOP+RIT					
9.03 (–11.75–29.80)	3.99 (1.59–6.38)*	3.03 (0.62–5.43)*	R10				
8.93 (–11.92–29.78)	3.89 (0.91–6.87)*	2.93 (–0.06–5.92)	–0.10 (–2.23–2.04)	R5			
4.95 (–15.78–25.68)	–0.09 (–2.03–1.85)	–1.05 (–3.01–0.91)	–4.08 (–5.47––2.68)*	–3.98 (–6.23––1.73)*	STD		
5.46 (–15.32–26.23)	0.42 (–1.94–2.77)	–0.54 (–2.91–1.82)	–3.57 (–5.49––1.65)*	–3.47 (–6.09––0.86)*	0.51 (–0.82–1.83)	TOCI	
D. Serious Adverse Events							
DEXA							
0.69 (0.17–2.80)	HCQ						
1.02 (0.32–3.28)	1.48 (0.52–4.21)	LOP+RIT					
0.86 (0.29–2.49)	1.24 (0.49–3.16)	0.84 (0.50–1.41)	R10				
0.59 (0.20–1.79)	0.86 (0.32–2.28)	0.58 (0.32–1.05)	0.69 (0.51–0.93)*	R5			
0.63 (0.22–1.80)	0.91 (0.36–2.28)	0.61 (0.37–1.00)	0.73 (0.61–0.87)*	1.06 (0.76–1.49)	STD		
0.82 (0.28–2.39)	1.19 (0.47–3.03)	0.80 (0.47–1.35)	0.96 (0.75–1.23)	1.39 (0.95–2.03)	1.31 (1.10–1.56)*	TOCI	

A: Effect estimate shown as RR with 95% CI; RR < 1 indicates the column treatment is better than the row treatment. * $P < .05$.

B: Effect estimate shown as RR with 95% CI, RR > 1 indicates the column treatment is better than the row treatment. * $P < .05$.

C: Effect estimate shown as mean difference in time to recovery with 95% CI, * $P < .05$.

D: Effect estimate shown as RR with 95% CI, RR < 1 indicates the column treatment is better than the row treatment. * $P < .05$.

CI, confidence interval; DEXA, dexamethasone; FAV, favipiravir; HCQ, hydroxychloroquine; INT, interferon- β ; LOP+RIT, lopinavir/ritonavir; R5, remdesivir for 5 days; R10, remdesivir for 10 days; RR, risk ratio; STD, standard care; TOCI, tocilizumab.

group (41.4%) among patients receiving invasive mechanical ventilation. The reduction in mortality of 10% with dexamethasone found in our study, although small, can be considered significant in view of the nature of illness and lack of effective therapies at present. In addition, a meta-analysis by Juul *et al.* and NMA by Diallo *et al.* have reported no effect of dexamethasone in reducing mortality.^{40,41}

Our NMA has found that remdesivir administered for 10 days was associated with increased clinical recovery by 10%, reduced time to clinical improvement by 4 days and lowered the occurrence of SAEs by 27% when compared to standard of care. However, there was no significant difference in mortality. Our results are similar to

the meta-analysis by Al-Abdoudh *et al.* who had reported that use of remdesivir in patients with moderate or severe COVID-19 infection was associated with significant increase in clinical recovery (risk difference [RD] 0.07; 95% CI 0.05 to 0.08; $P < .01$), hospital discharge (RD 0.07; 95% CI 0.03 to 0.11; $P = .02$) and lower occurrence of SAEs (RD –0.05; 95% CI –0.10 to –0.01; $P = .04$).^{42,43} An NMA by Siemieniuk *et al.* reported that, although remdesivir reduced the time to symptom resolution and duration of mechanical ventilation, it was not associated with any change in mortality.³⁸ Kim *et al.* in their NMA showed that remdesivir significantly reduced the mortality in moderate-to-severe COVID-19 patients while decreasing the rate of

TABLE 3 Ranking of interventions by P-score for all outcomes

Intervention	Mortality	Recovery	SAE	Time to clinical improvement
Remdesivir 200/100 mg for 10 d	0.92	0.91	0.66	0.89
Remdesivir 200/100 mg for 5 d	0.57	0.65	0.17	0.87
Dexamethasone	0.80	0.63	0.68	-
Standard care	0.52	0.11	0.21	0.25
Tocilizumab	0.21	0.20	0.59	0.41
Hydroxychloroquine	0.14	-	0.40	0.31
Favipiravir	-	-	-	0.27
Lopinavir + ritonavir	0.47	-	0.79	0.50
Interferon β	0.36	-	-	-

SAE, serious adverse events.

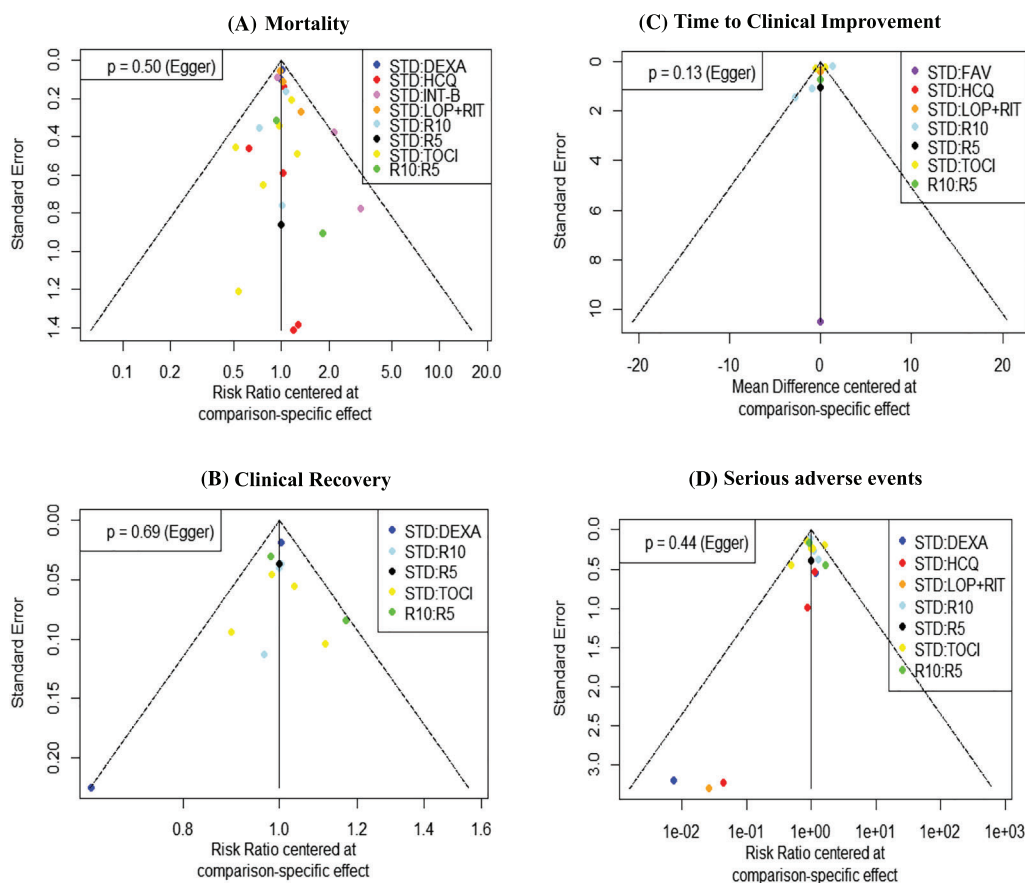


FIGURE 4 Funnel plot for outcomes. DEXA, dexamethasone; FAV, favipiravir; HCQ, hydroxychloroquine; LOP+RIT, lopinavir/ritonavir; R5, remdesivir for 5 days; R10, remdesivir for 10 days; STD, standard care; TOCI, tocilizumab

progression to severe disease.³⁷ In another meta-analysis, Juul *et al.* showed no survival benefit with remdesivir in addition to lack of information to confirm or reject that remdesivir reduces the risk of SAEs.⁴⁰ Nevertheless, Diallo *et al.* in their NMA reported that remdesivir administered for 10-days compared to standard care was associated with lower 28-day all-cause mortality (risk ratio 0.69, [0.48–0.99]) and serious AEs (risk ratio 0.48, 0.34–0.67), and higher clinical improvement (risk ratio 1.21 [1.00–1.47]).⁴¹

In our analysis, we have considered the 5- and 10-day treatments of remdesivir as separate entities, although most meta-analyses considered them together. Remdesivir, an antiviral drug that acts by inhibiting viral replication, was originally tested in Ebola. Remdesivir was initially granted an Emergency Use Authorization by the FDA for the treatment of hospitalized patients with suspected or confirmed severe COVID-19 infection, defined as oxygen saturation of 94% or less on room air or the need for supplemental oxygen. Following this,

the FDA updated their approval of remdesivir for use in adult and paediatric patients (age ≥ 12 y) requiring hospitalization.⁴ Central Drugs Standard Control Organisation (CDSCO) of India approved remdesivir under emergency use in June 2020.⁴⁴ National Institute of Health (NIH) COVID-19 guidelines state that the data is insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19 infection. However, it recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease.⁴⁵ Infectious Diseases Society of America guidelines recommend the use of remdesivir among hospitalized patients with severe COVID-19 infection (defined as patients with $SpO_2 \leq 94\%$ on room air, or patients who require supplemental oxygen, mechanical ventilation or extracorporeal mechanical oxygenation).⁴⁶ However, the WHO guidelines recommend against the use of remdesivir outside of clinical trials for COVID-19 of any disease severity.⁴⁷

Our NMA also found an increase in clinical recovery in the dexamethasone group by 6% (RR 1.06, CI [1.02–1.10]) as compared to the standard of care. This was driven largely by the results of RECOVERY trial which reported higher rates of discharges at 28 days amongst patients receiving dexamethasone (rate ratio, 1.10; 95% CI, 1.03–1.17). Similarly, in our study, time to clinical improvement was found to be significant only with remdesivir (both 5 and 10 d) while it was insignificant with other drugs namely favipiravir, lopinavir/ritonavir combination, tocilizumab and HCQ. These findings need to be considered carefully as time to clinical improvement is an acceptable endpoint in a pandemic situation where cases are rising exponentially and health care services are under severe strain.

Our NMA found that lopinavir and ritonavir combination, interferon β , tocilizumab and HCQ were not effective in reducing mortality in COVID-19 infection. These findings are similar to the results of living NMA.⁴⁰ Similarly, a meta-analysis done to evaluate the efficacy of HCQ from 11 RCTs, showed that HCQ does not have any effect on time to clinical improvement, or mortality in COVID-19 patients.⁴⁸ Similarly, in the RECOVERY trial, hospitalized patients with COVID-19 on HCQ did not show reduction in mortality at the end of 28 days compared to the standard care.⁴⁹

The present NMA found that drugs such as favipiravir, tocilizumab and HCQ were ineffective in improving clinical recovery. This is in concurrence to the study by Self *et al.* that found hospitalized adult COVID-19 patients, were not showing clinical improvement at the end of 14 days of treatment with HCQ, as compared to placebo.⁵⁰ A sensitivity analysis performed by excluding those studies with a mild–moderate population was consistent with findings of the overall analysis.

4.1 | Limitations

The present study could not assess the efficacy of newer drugs as it was done in the earlier part of the COVID-19 pandemic. Besides mortality, other endpoints such as the need for mechanical

ventilation/intubation were not assessed in our study due to the paucity of data. Further, the standard of care provided might have been different across the regions lacking uniformity. Nevertheless, during the initial part of the pandemic when these published studies were being conducted, there was no consensus on the standard of care prescribed across the globe.

4.2 | Strengths

This NMA was done exclusively from RCTs to avoid various bias included in the observational studies and to generate high-quality evidence. The study included only hospitalized patients with moderate to severe COVID-19 to reduce heterogeneity.

5 | CONCLUSION

This NMA of 23 randomised controlled trials done in hospitalized patients with moderate to severe COVID-19, found that dexamethasone reduces mortality and improves clinical recovery at the end of 28 days in comparison to standard of care. Likewise, remdesivir was significantly associated with a lower risk of mortality as compared to tocilizumab and had higher clinical recovery and shorter time to clinical improvement as compared to HCQ and tocilizumab. In addition, remdesivir and tocilizumab were associated with a lower occurrence of SAEs as compared to standard of care. As the pandemic is continuing, and various newer drugs and vaccines are being introduced to curb the disease, there is a need for NMA at a regular intervals to appraise the efficacy of the drugs used in COVID-19.

ACKNOWLEDGEMENTS

We thank Dr Mahalakshmi. G, Senior resident, Department of Clinical pharmacology; Dr Akila. S, Senior resident, Department of Clinical pharmacology and Mrs. Kothai Kumaran, Data entry operator, Department of Clinical Pharmacology for helping us with literature search.

COMPETING INTERESTS

None.

CONTRIBUTORS

S. Shivabasappa (S.S.2) and A.A. extracted the data, which were verified by S. Selvarajan (S.S.1). S.S.1 and M.G. were the primary and secondary reviewers and third reviewer (N.S.N.) was consulted around 20% of the time to arrive at a conclusion whenever there was a conflict between the primary and secondary reviewers. S.S.1 conceptualized the review; S.S.1, N.S.N. and A.A. drafted the study protocol; A.A. and S.S.1 were involved with literature search and study selection; M.G. and N.S.N. were involved with disagreement resolution and finalization of included studies; S.S.2 and A.A. performed the risk of bias analyses; S.S.2 and D.S. performed the analyses; S.S.1, S.S.2, M.G. and N.S.N. interpreted the analyses and wrote the results section; S.S.1, S.S.2, D.S., A.A. and M.G. drafted the review;

N.S.N. provided expert inputs and updated the final review. S.S.1 takes overall responsibility for this article as a corresponding author.

DATA AVAILABILITY STATEMENT

All relevant data are available in the article.

ORCID

Sandhiya Selvarajan  <https://orcid.org/0000-0002-7948-7821>

Annuja Anandaradje  <https://orcid.org/0000-0002-1020-1282>

Santhosh Shivabasappa  <https://orcid.org/0000-0001-7871-1038>

Deepthy Melepurakkal Sadanandan  <https://orcid.org/0000-0001-8547-2901>

N. Sreekumaran Nair  <https://orcid.org/0000-0002-0020-0796>

Melvin George  <https://orcid.org/0000-0001-7101-8513>

REFERENCES

- WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2021 Aug 23]. Available from: <https://covid19.who.int>
- Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis off Publ Infect Dis Soc Am*. 2020; 71(15):732-739. doi:10.1093/cid/ciaa237
- Bugatti S, Stefano LD, Bobbio-Pallavicini F, Montecucco C. Controversies over hydroxychloroquine in the prevention of SARS-CoV-2 infection put rheumatologists on the frontline. *RMD Open*. 2020;6(3):e001323. doi:10.1136/rmdopen-2020-001323
- FDA Approves First Treatment for COVID-19 [Internet]. FDA FDA; 2020 [cited 2021 Aug 23]. Available from: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19>
- WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511. doi:10.1056/NEJMoa2023184
- RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021; 384(8):693-704. doi:10.1056/NEJMoa2021436
- Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(8):e474-e484. doi:10.1016/S2665-9913(20)30173-9
- Parr JB. Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia. *JAMA Intern Med*. 2021;181(1):12-15. doi:10.1001/jamainternmed.2020.6557
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Assessing risk of bias in a randomized trial. *Cochrane Handb Syst Rev Interv Version 62 Cochrane Train 2021* [Internet]. Available from: <https://training.cochrane.org/handbook/current/chapter-08>
- Schwarzer G, Carpenter JR, Rücker G. Network Meta-Analysis. In: Schwarzer G, Carpenter JR, Rücker G, eds. *Meta-Analysis with R* [Internet]. Cham: Springer International Publishing; 2015 [cited 2022 Mar 14]. p. 187-216. (Use R!). Available from: 10.1007/978-3-319-21416-0_8.
- Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network Meta-Analysis Using R: A Review of Currently Available Automated Packages. *PLoS ONE*. 2014;9(12):e115065. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4277278/>
- Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS ONE*. 2013; 8(10):e76654. doi:10.1371/journal.pone.0076654
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
- Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15(1):58. doi:10.1186/s12874-015-0060-8
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109): 629-634. doi:10.1136/bmj.315.7109.629
- Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316. doi:10.1001/jama.2020.17021
- Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19): 1813-1826. doi:10.1056/NEJMoa2007764
- Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med*. 2020;383(19):1827-1837. doi:10.1056/NEJMoa2015301
- Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multi-centre trial. *Lancet Lond Engl*. 2020;395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9
- Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(11): 1048-1057. Available from: <https://pubmed.ncbi.nlm.nih.gov/32821939/>
- Hermine O, Mariette X, Tharoux PL, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*. 2021;181(1):32-40. Available from: <https://pubmed.ncbi.nlm.nih.gov/33080017/>
- Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*. 2021;181(1):24-31. doi:10.1001/jamainternmed.2020.6615
- Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med*. 2020;383(24): 2333-2344. doi:10.1056/NEJMoa2028836
- Rosas IO, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *N Engl J Med*. 2021; 384(16):1503-1516. doi:10.1056/NEJMoa2028700
- Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med*. 2021;384(1):20-30. doi:10.1056/NEJMoa2030340
- Vc V, Jagg P, Dlc F, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ*. 2021;372:n84. Available from: <https://pubmed.ncbi.nlm.nih.gov/33472855/>
- Ulrich RJ, Troxel AB, Carmody E, et al. Treating COVID-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind Randomized Controlled Trial in Hospitalized Patients. *Open Forum. Infect Dis*. 2020;7(10):ofaa446.
- Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ*. 2020;369:m1849. doi:10.1136/bmj.m1849
- Lyngbakken MN, Berdal JE, Eskesen A, et al. A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. *Nat Commun*. 2020;11(1): 5284. doi:10.1038/s41467-020-19056-6
- Abd-Elsalam S, Esmail ES, Khalaf M, et al. Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled

- Study. *Am J Trop Med Hyg.* 2020;103(4):1635-1639. doi:10.4269/ajtmh.20-0873
31. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med.* 2020;383(21):2041-2052. doi:10.1056/NEJMoa2019014
 32. Lou Y, Liu L, Yao H, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. *Eur J Pharm Sci off J Eur Fed Pharm Sci.* 2021;157:105631. doi:10.1016/j.ejps.2020.105631
 33. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Lond Engl.* 2020;396(10259):1345-1352. doi:10.1016/S0140-6736(20)32013-4
 34. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med.* 2020;382(19):1787-1799. doi:10.1056/NEJMoa2001282
 35. Davoudi-Monfared E, Rahmani H, Khalili H, et al. A Randomized Clinical Trial of the Efficacy and Safety of Interferon β -1a in Treatment of Severe COVID-19. *Antimicrob Agents Chemother.* 2020;64(9):e01061-e01020. doi:10.1128/AAC.01061-20
 36. Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon β -1b in treatment of severe COVID-19: A randomized clinical trial. *Int Immunopharmacol.* 2020;88:106903. doi:10.1016/j.intimp.2020.106903
 37. Kim MS, An MH, Kim WJ, Hwang T-H. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. *PLoS Med.* 2020;17(12):e1003501. doi:10.1371/journal.pmed.1003501
 38. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ.* 2020;370:m2980.
 39. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA.* 2020;324(13):1330-1341.
 40. Juul S, Nielsen EE, Feinberg J, et al. Interventions for treatment of COVID-19: A living systematic review with meta-analyses and trial sequential analyses (The LIVING Project). *PLoS Med.* 2020;17(9):e1003293. doi:10.1371/journal.pmed.1003293
 41. Diallo A, Carlos-Bolumbu M, Traoré M, Diallo MH, Jedrecy C. An updated systematic review and network meta-analysis of 25 randomized trials assessing the efficacy and safety of treatments in COVID-19 disease. *J Public Health Res.* 2021;10(1):1945. doi:10.4081/jphr.2021.1945
 42. Al-Abdoun A, Bizanti A, Barbarawi M, et al. Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Contemp Clin Trials.* 2021;101:106272. doi:10.1016/j.cct.2021.106272
 43. Kaka AS, MacDonald R, Greer N, et al. Major Update: Remdesivir for Adults With COVID-19: A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points. *Ann Intern Med.* 2021;174(5):663-672. doi:10.7326/M20-8148
 44. COVID-19 Updates [Internet]. [cited 2021 Aug 23]. Available from: <https://pib.gov.in/pib.gov.in/Pressreleaseshare.aspx?PRID=1631509>
 45. Information on COVID-19 Treatment, Prevention and Research [Internet]. COVID-19 Treatment Guidelines. [cited 2021 Aug 23]. Available from: <https://www.covid19treatmentguidelines.nih.gov/>
 46. IDSA Guidelines on the Treatment and Management of Patients with COVID-19 [Internet]. [cited 2021 Aug 23]. Available from: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-8>
 47. COVID-19 Clinical management: living guidance [Internet]. [cited 2021 Aug 23]. Available from: <https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-clinical-2021-1>
 48. Amani B, Khanijahani A, Amani B. Hydroxychloroquine plus standard of care compared with standard of care alone in COVID-19: a meta-analysis of randomized controlled trials. *Sci Rep.* 2021;11(1):11974. doi:10.1038/s41598-021-91089-3
 49. RECOVERY Collaborative Group, Horby P, Mafham M, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med.* 2020;383(21):2030-2040. doi:10.1056/NEJMoa2022926
 50. Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(21):2165-2176. doi:10.1001/jama.2020.22240

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Selvarajan S, Anandaradje A, Shivabasappa S, Melepurakkal Sadanandan D, Nair NS, George M. Efficacy of pharmacological interventions in COVID-19: A network meta-analysis. *Br J Clin Pharmacol.* 2022;1-12. doi:10.1111/bcp.15338