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Efficacy and safety of Remdesivir in COVID-19 caused by SARS-CoV-2: A systematic review and meta-analysis

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Title: Efficacy and safety of Remdesivir in COVID-19 caused by SARS-CoV-2: A systematic review and meta-analysis

Running title : Effectiveness of Remdesivir in COVID-19

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Title: Efficacy and safety of Remdesivir in COVID-19 caused by SARS-CoV-2: A systematic review and meta-analysis

ABSTRACT

Objectives: Remdesivir, an RNA polymerase inhibitor, evaluated for effectiveness in comparison to Standard therapy in adult COVID-19 patients.

Data sources: Electronic search for eligible articles of Medline (via PubMed), The Cochrane Central Register of Controlled Trials, and clinicaltrials.gov was done.

Participants & study eligibility criteria: Only RCTs aimed to evaluate the efficacy of Remdesivir in the treatment COVID-19 were considered eligible for this systematic review.

Interventions: Remdesivir was compared with standard of care, which acts as control group

Primary and secondary outcomes: Primary outcomes was mortality and secondary outcomes were time to clinical improvement and safety outcomes like serious adverse events, respiratory failure

Study appraisal and synthesis methods: Meta-analysis was performed by Cochrane review manager 5 (RevMan) version 5.3. Cochrane risk of bias 2.0 tool was used for methodological quality assessment. The GRADE pro GDT was applied for overall quality of evidence.

Results: 52 RCTs were screened and 4 studies were included in analysis, with total of 7324 patients. No mortality benefit with use of remdesivir versus standard of care [OR=0.92 (95%CI = 0.79 – 1.07), p=0.30, moderate quality evidence]. Significant clinical improvement [OR=1.52 (95%CI = 1.24 – 1.87), p<0.0001, low quality] and time to clinical improvement [HR=1.28 (95%CI = 1.12 – 1.46), p=0.0002, very low quality] with the use of remdesivir versus control group. Significant decrease was found in the risk of serious adverse events[RR=0.75 (95%CI = 0.62 – 0.90), p=0.0003, low quality], however no difference was

found in the risk of respiratory failure [RR=0.85 (95%CI = 0.41 – 1.77), p=0.67, very low quality evidence] with remdesivir.

Conclusions: With the current evidence on efficacy and safety of remdesivir, authors do not recommend use of Remdesivir for treatment for COVID-19 patients caused by SARS-CoV-2, as it has shown no mortality benefit (moderate quality evidence) and cost-benefit analysis revealed limited use especially in developing countries.

Systematic review registration: PROSPERO registration number: CRD42020189517

Keywords: Remdesivir, COVID-19, SARS-CoV-2

Article Summary

Strengths and Limitations of this study

- There is preliminary evidence of clinical benefit and approval of remdesivir as compassionate use by US FDA in COVID-19 patients.
- Our study showed No Mortality benefit with the use of Remdesivir in COVID-19 patients, with moderate quality evidence.
- Subgroup analysis showed No mortality benefit in patients with or without requirement of assisted ventilation.
- Benefit in time to clinical improvement but with “Very low” quality of evidence. Systematic review indicates no benefit with the use of remdesivir in COVID-19 patients.
- Overall evidence suggests no beneficial effect and thus recommend against the use of remdesivir, especially in lower to middle income countries.

INTRODUCTION

A novel coronavirus disease (COVID-19), caused by infection with SARS-CoV-2, created a pandemic of mortality all over the world.[1, 2] The global pandemic of SARS-CoV-2 infections has affected more than 3.8 million people world-wide and has been the cause of 1.08 million deaths globally by the 10th of October 2020 as per COVID-19 statistics data. Twenty six million people have recovered and as the trend suggests most of them either stay asymptomatic and few of them develop pneumonia like symptoms that does not require oxygen support.[3] A very small percentage get critical to the limit of hypoxia, acute respiratory distress syndrome and multi- organ failure. Among these critical patients who are being put on mechanical ventilation, half of them die.

The search for an effective therapy or preventive modality has become the utmost need of the hour. There are few proposed and approved drugs with some antiviral action and they are under investigation simultaneously across the globe. But as yet no proven effective therapy for SARS -CoV-2 has been accepted widely. Amongst the few promising therapies available remdesivir, a viral RNA polymerase inhibitor has been recommended by US FDA as a drug for compassionate use for treatment of COVID-19 patients. Remdesivir, a nucleoside analogue prodrug, has shown inhibitory effects on SARS-CoV-2, both in vitro and in animal models. However even for the above mentioned studies, contrasting results have been reported in different nations like China and USA.[3] Varied study designs[4, 5], genetic reasons and different treatment regimens (5 or 10 days) have been attributed for this difference.

Only two randomized controlled clinical trials (RCT) have shown efficacy of remdesivir in COVID-19 patients. Many RCTs are undergoing to assess the benefit-risk ratio of remdesivir.

Current review was planned to assess the mortality and clinical benefit in addition to safety of remdesivir in the treatment of COVID-19 caused by SARS-CoV-2.

METHODS

Protocol and registration

The present systematic review was done as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The protocol has been registered with PROSPERO (International Prospective Register of Systematic Reviews) database; protocol number as CRD42020189517.

Criteria for study inclusion

Only RCTs evaluating role of remdesivir compared to standard care in COVID-19 were included. Observational studies, review articles, case reports or case series were excluded.

Search strategy and study selection

Electronic literature search using Medline (via PubMed), The Cochrane Central Register of Controlled Trials and clinicaltrials.gov was conducted on 20th September 2020, to identify all the published relevant articles. Bibliographic search of published articles were also done manually to identify more studies. Language or publication status restriction was applied. Search strategy using following medical subject headings (MeSH) was developed: 'SARS-CoV-2', 'COVID-19', 'Remdesivir', 'COVID', 'novel coronavirus'. RCT restriction was applied.

The titles and abstracts retrieved by electronic searching were assessed by two independent researchers for potential eligibility and duplicates removed.

Data extraction

Study design, remdesivir doses and regimens, total subjects along with their characteristics, efficacy and safety outcomes were extracted on pre-structured form.

Study outcomes

The primary outcome included in our review was mortality (defined as deaths in each group). The secondary outcomes were clinical improvement and virological cure. In addition serious adverse events and other safety parameters were assessed.

Quality assessment of studies

Two authors independently (DK and AC) assessed the methodological quality of included studies. Cochrane Collaboration risk of bias 2 tool (ROB-2) [6] was used. Overall assessment was recorded as high, low and some concerns. Robvis (visualization tool)[7] was used for synthesis of plots for risk of bias.[7]

For publication bias assessment, funnel plot asymmetry was not assessed as studies were less than five. However, Egger's regression test was applied.

Data synthesis and summary measures

Dichotomous data were summarized as odd ratios (OR) and adjusted hazard ratios (HR) with 95% confidence intervals (CI) wherever applicable. Review Manager 5 (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all the analyses.[8] Heterogeneity was assessed using I^2 [9, 10]. The results of both fixed and random effect model were assessed for interpretation [9, 11].

Assessment of Quality of Evidence - GRADE Pro analysis

The overall quality of evidence for each of the outcomes was assessed using GRADE pro GDT (guideline development tool) software based on the principles of Grades of Recommendations, Assessment, Development and Evaluation (GRADE).[12] Optimal information size (OIS) was calculated to be 1213 patients in each group. Final overall

GRADE may be high, moderate, low or very low. The online version of GRADE pro GDT software was accessed from the site: https://gradepro.org/. [12]

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

RESULTS

Study selection

The study selection and exclusion process has been documented using the PRISMA flow diagram (Figure 1). Out of total 52 records screened, 4 RCTs[3, 13, 14] were included in analysis.

Study characteristics

Study characteristics of RCTs of present systematic review are mentioned in Table 1.

Risk of bias (ROB) within the studies

The overall risk of bias was assessed as "Low" as WHO solidarity trial[14] and Wang et al.[3] ROB was assessed as low. Study done by Beigel et al[13] and Spinner et al.[15] was regarded as having "High" ROB. Hence, ROB assessed for outcomes having data only from Beigel et al. and Spinner et al. in GRADE analysis was regarded as having serious issues. The ROB of RCTs was represented in Figure 2 and Supplementary Figure 1 (Weighted summary ROB).

Efficacy outcomes

Mortality

Mortality data was included from 4 RCTs with 3818 and 3506 patients in Remdesivir and standard of care groups, respectively. Remdesivir has no mortality benefit as compared to control group [OR=0.92 (95%CI = 0.79 – 1.07), p=0.30; I^2=0] (Figure 3a). Sub-group

analysis revealed no mortality benefit in low risk and high groups (Figure 3a, Supplementary Figure 2)

Clinical Improvement

Statistically significant increase in rates of clinical improvement in remdesivir versus controls was found [OR=1.52 (95%CI = 1.24 – 1.87), p<0.0001; I^2=0%] (Figure 3b). Results were drawn from 3 RCTs with total of 1879 patients.

Time to clinical improvement

Pooled analysis revealed that there was significant increase in the time to clinical improvement in remdesivir group as compared to controls [HR=1.28 (95%CI = 1.12 – 1.46), p=0.0002; I^2=0%](Figure 3c). Data extracted from 2 RCTs with total of 1292 patients.

Safety outcomes

Serious Adverse Events (AE)

Pooled analysis revealed significant increase in the risk of serious adverse events in control group as compared to remdesivir [RR=0.75 (95%CI = 0.62 – 0.90), p=0.0003; I^2=0%] (Figure 4a). This data was extracted from 3 RCTs with a total of 1875 patients.

Respiratory Failure

No difference in the risk of respiratory failure between remdesivir and control groups was found [RR=0.85 (95%CI = 0.41 – 1.77), p=0.67; I^2=55%] (Figure 4b). Findings were derived from 2 RCTs with a total of 1291 patients.

Publication bias

Though the funnel plot asymmetry was not assessed. The Egger's regression test applied on four studies included in mortality rate assessment showed no publication bias (t = - 0.5947, p = 0.6123).

GRADE analysis of the primary and secondary outcomes (Table 2)

The GRADE analysis recommendation for mortality was 'Moderate' evidence quality. Though there is low ROB, low heterogeneity and direct outcome but there are serious concerns with imprecision. The quality of evidence for clinical improvement and time to clinical improvement were graded as "Low" and "Very Low" respectively. The GRADE recommendation for serious AE and respiratory failure were "Low" and "Very low" quality of evidence respectively, as there was presence of high ROB and high imprecision. The GRADE recommendation is shown in table 2.

Discussion

With the existing recommendation of USFDA for compassionate use of Remdesivir in COVID patients, it is being used worldwide. Current systematic review was planned for recommendation drawn from RCTs evaluating the efficacy of remdesivir in COVID-19 patients.

In the current systematic review, ORs for mortality was unable to confer any mortality benefit with the use of remdesivir. WHO solidarity trial[14] showed no mortality benefit with the use of remdesivir. Though it was an open label study, it is less likely to have bias in assessment of objective outcome like mortality. A total of 3451 patients were included in remdesivir and standard of care groups. Subgroup analysis revealed no mortality benefit in low risk (Figure 3a - no oxygen requirement, Supplementary Figure 2 – No invasive ventilation) or high risk (Figure 3a - oxygen requirement or assisted ventilation, Supplementary Figure 2 – Invasive ventilation) group of patients with remdesivir.

At the time of recruitment, more patients were on invasive mechanical ventilation or ECMO in the placebo group. There were significantly more number of serious adverse events

reported in our review due to increase serious AE in Beigel et al study.[13] This is rare occurrence that serious AE were significantly more in control group. The fact that more severe patients were randomized into control group in the study by Beigel et al.[13] is the major reason for this finding. Similarly, the serious AE which also included the clinical events like renal failure and respiratory failure (5.2% in remdesivir and 8% in placebo arm) were also observed more in placebo group. Despite this imbalance, remdesivir was unable to show superiority in mortality rate.

Sub-group analysis of Beigel et al.[13] study revealed that remdesivir resulted in significant rate of clinical improvement in COVID-19 patients on oxygen therapy, while the patients not on oxygen, or on high flow oxygen or non-invasive ventilation and receiving mechanical ventilation or ECMO had similar clinical improvement as standard of care.

Placebo used in Beigel et al.[13] study was sulfo-butyl-ether b-cyclodextrin-sodium (SBECD), used to dissolve remdesivir. The maximum recommended daily dose is approximately 250 mg/kg solvent used to dissolve remdesivir.[13] The amount of solvent present in placebo was not quantified in protocol. Dose of solvent should be modified in patients with eGFR fall of more than 50% from baseline and is contraindicated in patients with eGFR less than 30ml/min. But such modification were not done in either arms. Hence the effect of solvent on patients with impaired renal function can be detrimental and cannot be ruled out.

In the study by Beigel et al.[13], the median time of administration of drug from randomization was nine days. Median recovery time from randomization was 11 days. In addition, 302 patients in remdesivir group did not receive 10 days of treatment. Therefore, it is difficult to infer that the remdesivir has resulted in recovery of patients, as average 2 days of administration resulting in complete recovery of patients is impossible.

The virological cure is the most important outcome which was neglected by the authors. Wang et al reported no difference (percentage difference = -7.5 (95% CI = -19.2 to 4.2)) in undetectable viral RNA load in remdesivir (75.6%) and placebo groups (83.1%). Patients may become asymptomatic but not cured. It has been observed that asymptomatic patients with RT-PCR positive test can have thromboembolic and chest CT changes. Study done by Merkler et al observed that eight patients (26%) out of total 31 ischemic stroke patients presented with ischemic stroke. They didn't have any COVID-19 symptoms on presentation.[16]

The SIMPLE trial[4] results published in New England Journal of Medicine does not include a standard of care group. Similar to Beigel et al. virological cure was not reported.[4] Clinical status at day 14 was similar in 5 day course of remdesivir as compared to 10 day course. However, in comparison to standard care, 5 day group (OR 1.65 [95% CI 1.09-2.48]; p=0.017) showed significant improvement while 10 day group did not (OR 1.31 [95% CI 0.88-1.95]; p=0.18). Death reported on day 11 was similar in all three groups.[17]

In another study published by Grein et al.[5] on compassionate use of remdesivir did not have a control arm. Hence, the conclusion that remdesivir is effective cannot be drawn as the possibility of observing similar findings in control arm cannot be ruled out.

Three systematic reviews and meta-analysis were published on remdesivir[18-20]. However, none of the reviews have included WHO solidarity trials in review. Exclusion of such large study (N=3451) decreases the power of systematic reviews. Our results are different from all three systematic reviews as Wilt et al.[20] and Shrestha et al.[18] have concluded mortality benefit with remdesivir while Elsawah et al.[19] concluded significant clinical improvement with remdesivir as compared to standard care.

The cost of the drug is $2340 per patient and with no mortality benefit. From a cost benefit perspective, it is our personal opinion that it should not be recommended for use, especially in developing countries.[21]

Limitations and strengths

A major strength of our systematic review is that four RCTs were included in our analysis with total sample size of 7324 patients. Study done by Wang et al and WHO Solidarity trial has low ROB. Robust method of analysis using ROB-2 and GARDE analysis is another strength of the current systematic review.

Quality of Evidence: (GRADE)

The overall quality of systematic review is "Moderate". Critical outcomes like mortality has moderate quality evidence. Clinical improvement was regarded as "Low". Time to clinical improvement has "Very low" quality of evidence. Time to clinical improvement was used by regulatory agencies like US FDA for giving approval to remdesivir for treatment of severe COVID-19 patients. Hence, the quality of evidence for time to clinical improvement cannot be overlooked. This evidence suggests that further research is very likely to have an important impact on our confidence in the estimate of time to clinical improvement and likely to change the estimate. Moderate quality of evidence with regard to mortality showed that further RCTs are likely to have important impact and may change the no mortality benefit conclusion drawn from review.

Conclusion:

Evidence of our systematic review indicates no benefit in mortality rate with remdesivir, with moderate quality of evidence. Benefit does exist in terms of clinical improvement and time to clinical improvement, but the evidence is of low and very low quality. Significant decrease in

serious adverse events as compared to placebo, strengthens the evidence of more serious patients in placebo arm. No difference was shown in respiratory failure in the two groups (very low quality evidence). All outcomes except mortality in our meta-analysis were influenced by Beigel et al. and Spinner et al., which has high ROB. WHO solidarity trial and Wang et al showed no mortality benefit, both having overall low ROB.

Abbreviation List

COVID-Corona Virus Disease

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - International Prospective Register of Systematic Reviews

ROB-2 - The Risk Of Bias -2 tool for randomized control trials

CI: Confidence interval

OR - Odd ratios

HR - Hazard ratios

GRADE pro GDT - Grades of Recommendations, Assessment, Development and Evaluations (GRADE) guideline development tool

OIS - Optimal information size

Declarations

Ethical approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of supporting Data: The datasets used and/or analyzed during the current study are available from the corresponding author on request

Competing Interests: Dr. SINGH has nothing to disclose. Dr. CHUGH A has nothing to disclose. Dr Khera D has nothing to disclose. Dr Khera P has nothing to disclose. Dr. CHUGH V has nothing to disclose.

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Authors Contribution:

Study design and planning of systematic review - All of the authors

Literature search - AC, SS

Figures – SS, VKC, AC

Tables - DK, SS

Data collection and analysis - SS, DK

ROB - DK, AC, SS, Query resolved by all authors

GRADE Analysis - SS, AC, DK, Query resolved by all authors

Data interpretation -, SS, DK, AC

Writing - SS, DK, AC

Corrections and Final approval of Manuscript - All of the authors

The corresponding author attests that all listed authors meet authorship criteria as per ICJME and that the manuscript is an honest, accurate, and transparent account of the study being reported

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Table 1. Characteristics of clinical studies evaluating Remdesivir for treatment of COVID-19

Author, year (Study design)	Institution/ Country of study conduct	Study Interventions (N)/ Regimen	Study control (N)/ Regimen	Study population characteristics	Study outcomes
Beigel et al 2020 (Randomized controlled trial)	Multicenter trial	Remdesivir (538); 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	Placebo (521)	Hospitalized adult COVID-19 patients with evidence of lower respiratory tract involvement.	**Time to recovery:** Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% confidence interval [CI], 1.12 to 1.55; P<0.001 **Mortality:** Kaplan Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04)
Spinner et al	Multicenter trial	Remdesivir - 10-day (n = 197), Remdesivir - 5-day (n = 199)	Standard care (n = 200)	Confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%)	**Day 28** Mortality rate n(%) – Remdesivir 10 day = 3(2); Remdesivir 5 day = 2(1), Standard = 4(2) Clinical Improvement n(%) - Remdesivir 10 day =174((90), Remdesivir 5 day = 171(90), Standard = 166(83)
Wang et al 2020 (Randomized controlled trial)	Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital,	Remdesivir (158); at least 1 dose after entering ICU; 200 mg on day 1 followed by 100 mg on days 2–10 in	Placebo (79)	Hospitalized adult COVID-19 patients with symptom onset to enrolment interval of ≤ 12 days, oxygen saturation ≤ 94% on room air or a ratio of arterial oxygen partial pressure to fractional	**Time to clinical improvement within 28 days after randomization:** Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]

	Beijing, China	single daily infusions		inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia	**28-day mortality:** similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI –8·1 to 10·3]).
WHO Solidarity Trial 2020 (Randomized controlled trial)	World Health Organization, Multicentric trial (405 hospitals in 30 countries)	Remdesivir (2743); Day 0, 200mg; days 1-9, 100mg	Placebo (2708)	Hospitalized with a diagnosis of COVID-19, age ≥18 years, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours	**Mortality rate:** Remdesivir RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control). Hydroxychloroquine RR=1.19 (0.89-1.59, p=0.23; 104/947 vs 84/906), Lopinavir RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372) Interferon RR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050)

Table 2: GRADE recommendation for primary and secondary outcomes of use of Remdesivir in COVID-19

Certainty assessment						№ of patients		Effect		Certainty Importance
№ of studies Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Efficacy and Safety of Remdesivir**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Mortality at day 28										
4 RCT	not serious [a]	not serious	not serious	serious [b]	none	387/3818 (10.1%)	394/3506 (11.2%)	**OR 0.92** (0.79 to 1.07)	**8 fewer per 1,000** (from 21 fewer to 7 more)	⨁⨁⨁◯ MODERATE CRITICAL
Clinical Improvement										
3 RCT	serious [c]	not serious	not serious	serious [d]	none	782/1080 (72.4%)	484/799 (60.6%)	**OR 1.52** (1.24 to 1.87)	**94 more per 1,000** (from 50 more to 136 more)	⨁⨁◯◯ LOW IMPORTANT
Time to clinical Improvement										
2 RCT	serious [e]	not serious	serious [f]	serious [d]	none	-/0	-/0	**HR 1.28** (1.12 to 1.46)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁◯◯◯ VERY LOW IMPORTANT
Serious Adverse events										
3 RCT	serious [c]	not serious	not serious	serious [d]	none	161/1075 (15.0%)	179/800 (22.4%)	**RR 0.75** (0.62 to 0.90)	**56 fewer per 1,000** (from 85 fewer to 22 fewer)	⨁⨁◯◯ LOW IMPORTANT
Respiratory Failure										
2 RCT	serious [e]	serious [g]	not serious	serious [h]	none	44/691 (6.4%)	48/600 (8.0%)	**RR 0.85** (0.41 to 1.77)	**12 fewer per 1,000** (from 47 fewer to 62 more)	⨁◯◯◯ VERY LOW CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio; **RR:** Risk ratio; RCT – Randomized controlled trials

Explanations

a. All studies have low ROB except Biegel et al. WHO solidarity trial contributes 77.9% weight to overall effect has low ROB. Hence overall low ROB.

b. Overall information size of 1213 was achieved in either group. However, the overall effect estimate included one, hence downgraded for imprecision

c. Biegel et al. and Spinner et al. have a high risk of bias (ROB) due to selective reporting of results. Hence, downgraded for ROB.

d. Overall Information Size of 1213 was not achieved in either groups. Hence, downgraded for imprecision

e. Biegel et al. has a high risk of bias (ROB) due to selective reporting of results. Hence, downgraded for ROB.

f. Time to clinical improvement is not a direct estimate of the patient's oriented outcomes. Hence, downgraded for evidence

g. As I2 >50%, heterogeneity is significantly high. Hence, downgraded for Inconsistency

h. Overall information size of 1213 was not achieved in either group and the overall effect estimate included one, hence downgraded for imprecision

Captions for Figures

Figure 1: PRISMA flow chart depicting study selection process

Figure 2: ROB-2: Risk of bias in RCT evaluating Remdesivir for treatment of COVID-19

Figure 3: Mortality rate (3a), clinical improvement (3b) and time to clinical improvement (3c) of remdesivir vs control treatment

Figure 4: Number of patients with Serious adverse events (4a) and respiratory failure (4b) (remdesivir vs control treatment)

Supplementary Figure 1: ROB-2: Risk of bias of RCT evaluating remdesivir in COVID-19 (Weighted Summary plot)

Supplementary Figure 2: Forest plot of mortality rates in low risk (with or without O2) versus high risk (Invasive ventilation) Groups for use of remdesivir versus standard of care in COVID-19

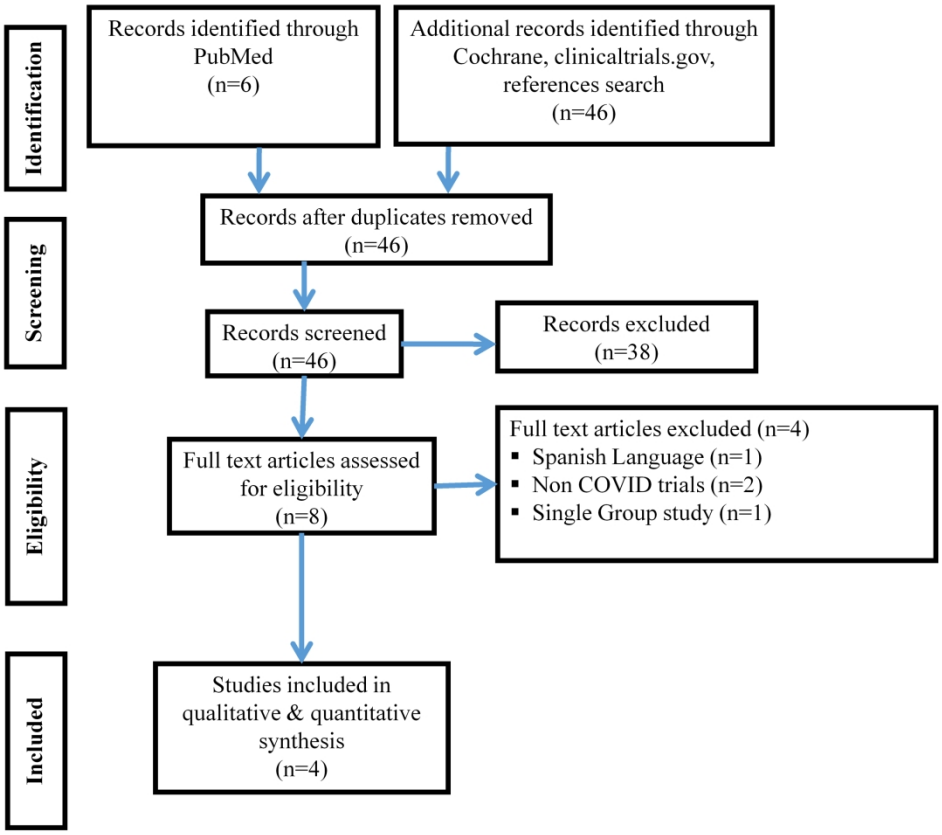

Figure 1: PRISMA flow chart depicting study selection process

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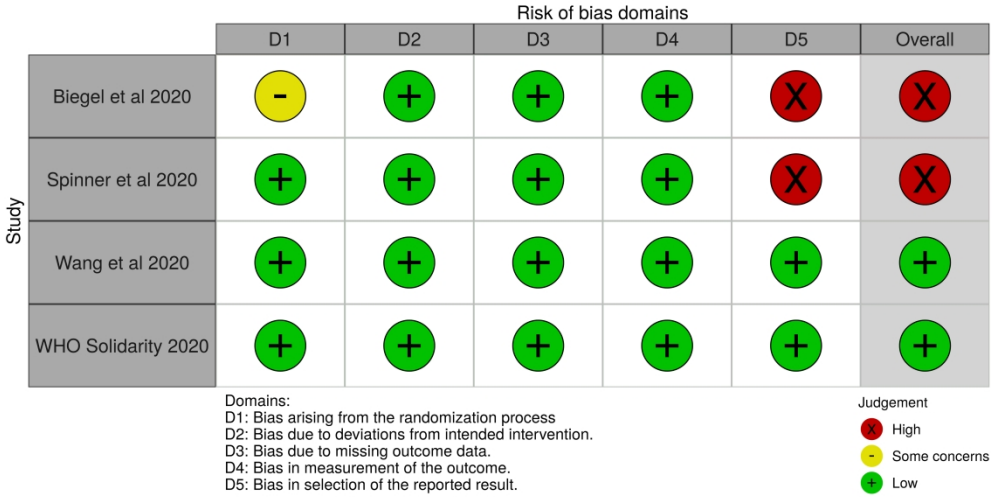


Figure 2: ROB-2: Risk of bias in RCT evaluating Remdesivir for treatment of COVID-19

227x127mm (600 x 600 DPI)

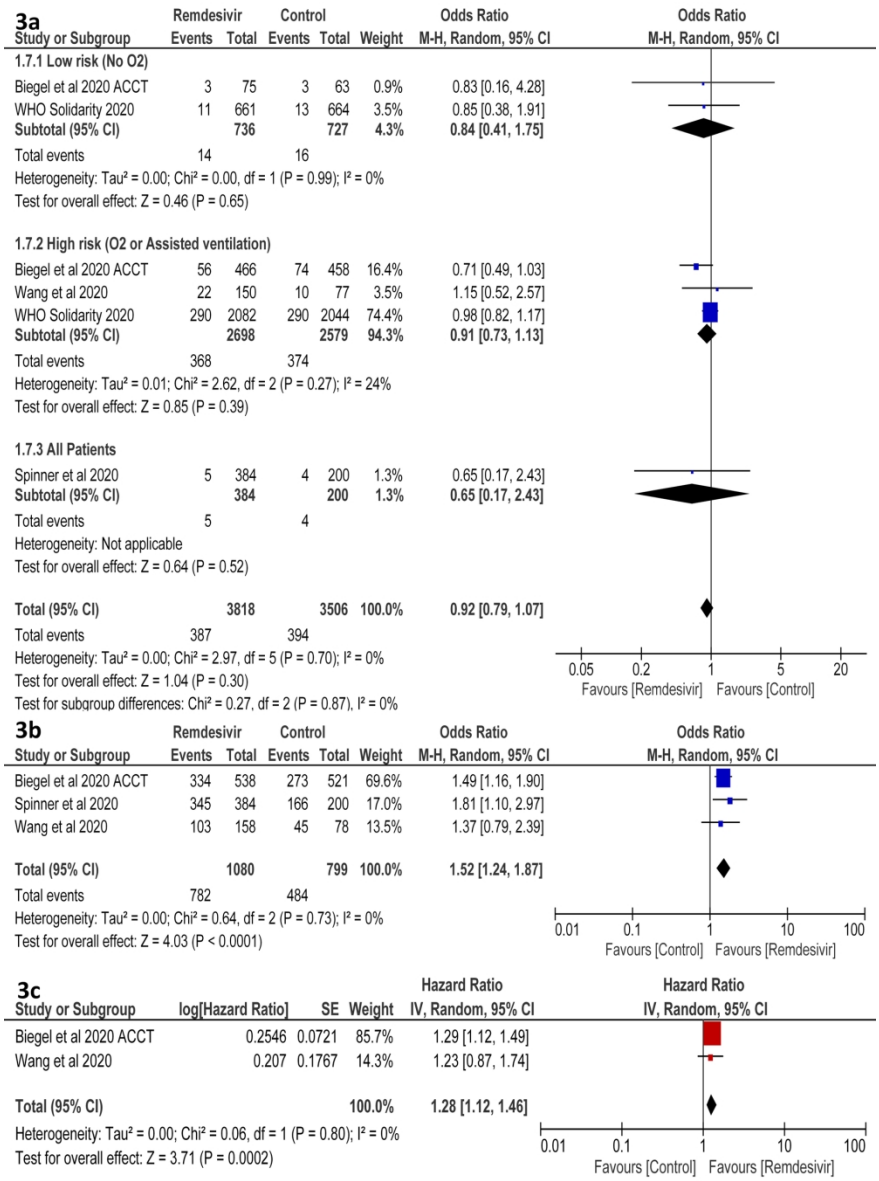


Figure 3: Mortality rate (3a), clinical improvement (3b) and time to clinical improvement (3c) of remdesivir vs control treatment

158x218mm (300 x 300 DPI)

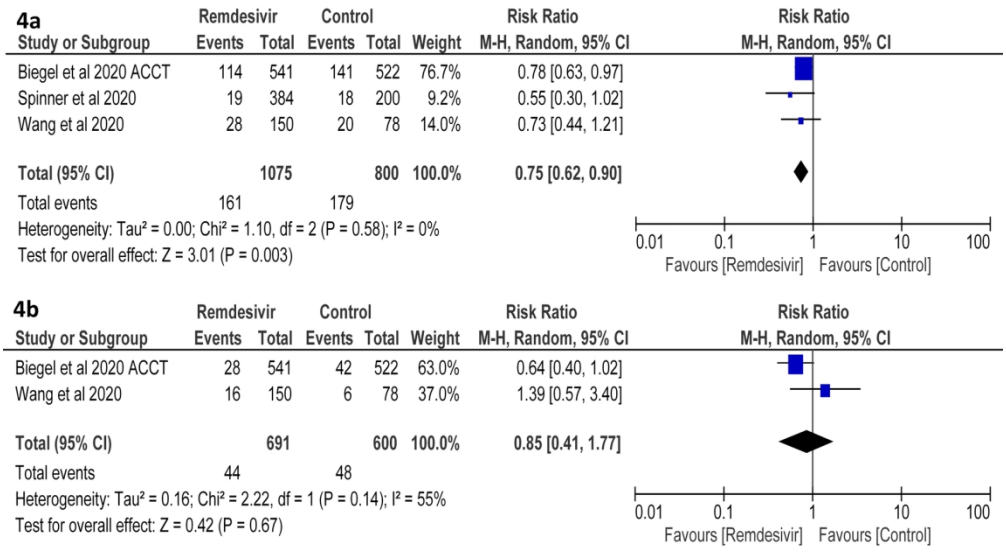
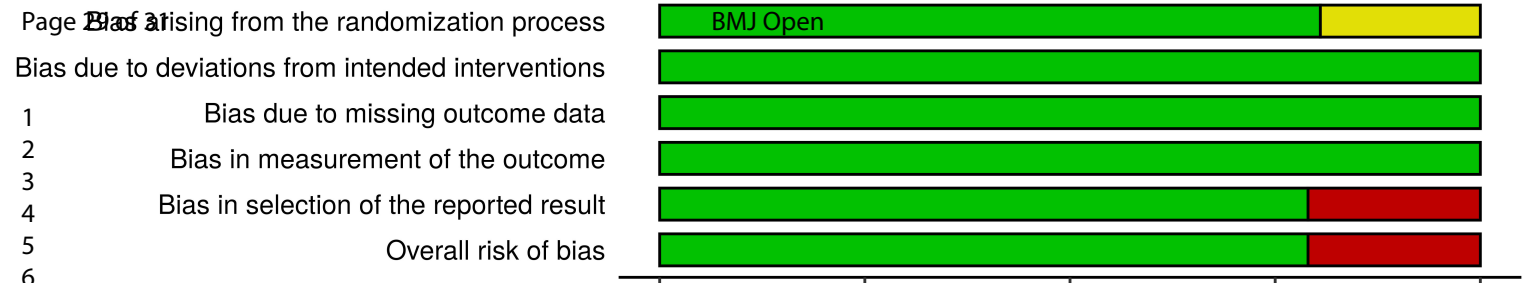


Figure 4: Number of patients with Serious adverse events (4a) and respiratory failure (4b) (remdesivir vs control treatment)

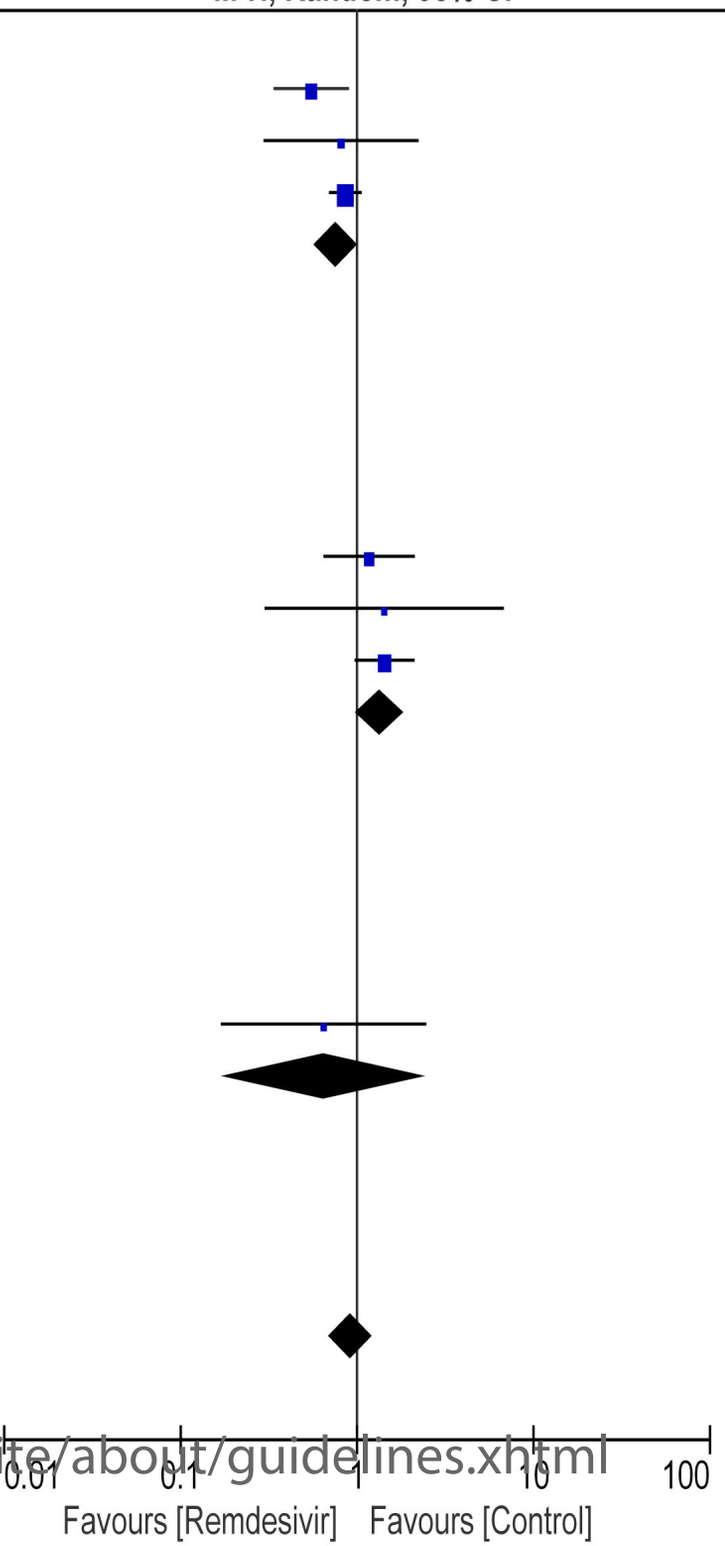
158x89mm (300 x 300 DPI)

Supplementary Figure 1: ROB-2: Risk of bias of RCT evaluating remdesivir in COVID-19 (Weighted Summary plot)



Supplementary Figure 2: Forest plot of mortality rates in low risk (with or without O2) versus high risk (Invasive ventilation) Groups for use of remdesivir versus standard of care in COVID-19

Study or Subgroup	Remdesivir Events	Remdesivir Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.8.1 Low risk (O2 but no Invasive ventilation)						
Biegel et al 2020 ACCT	31	402	48	364	18.1%	0.55 [0.34, 0.89]
Wang et al 2020	11	129	7	68	6.7%	0.81 [0.30, 2.20]
WHO Solidarity 2020	203	2489	232	2475	30.9%	0.86 [0.70, 1.05]
Subtotal (95% CI)		**3020**		**2907**	**55.8%**	**0.76 [0.56, 1.02]**
Total events	245		287			
Heterogeneity: Tau² = 0.02; Chi² = 2.87, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 1.85 (P = 0.06)						
1.8.2 High Risk (Invasive ventilation)						
Biegel et al 2020 ACCT	28	131	29	154	14.6%	1.17 [0.66, 2.10]
Wang et al 2020	11	29	3	10	3.1%	1.43 [0.30, 6.70]
WHO Solidarity 2020	98	254	71	233	22.3%	1.43 [0.98, 2.09]
Subtotal (95% CI)		**414**		**397**	**40.0%**	**1.35 [0.99, 1.84]**
Total events	137		103			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.06)						
1.8.3 All Patients						
Spinner et al 2020	5	384	4	200	4.1%	0.65 [0.17, 2.43]
Subtotal (95% CI)		**384**		**200**	**4.1%**	**0.65 [0.17, 2.43]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**3818**		**3504**	**100.0%**	**0.93 [0.70, 1.24]**
Total events	387		394			
Heterogeneity: Tau² = 0.06; Chi² = 11.59, df = 6 (P = 0.07); I² = 48%						
Test for overall effect: Z = 0.50 (P = 0.62)						
Test for subgroup differences: Chi² = 7.48, df = 2 (P = 0.02), I² = 73.3%						



*In ventilation subgroup, Wang et al study included patients on high flow oxygen in addition to invasive ventilation

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12, 4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Efficacy and safety of Remdesivir in COVID-19 caused by SARS-CoV-2: A systematic review and meta-analysis

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Emergency medicine, Evidence based practice, Respiratory medicine, Medical management
Keywords:	COVID-19, Immunology < NATURAL SCIENCE DISCIPLINES, CLINICAL PHARMACOLOGY, Respiratory infections < THORACIC MEDICINE

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Title: Efficacy and safety of Remdesivir in COVID-19 caused by SARS-CoV-2: A systematic review and meta-analysis

Running title : Effectiveness of Remdesivir in COVID-19

Authors: Surjit Singh, D.M[1], Daisy Khera, M.D[2], Ankita Chugh, MDS[3], Pushpinder Singh Khera[4], Vinay Kumar Chugh[5]

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Word counts - 2592

for abstract: 248

for the text: 2344

Title: Efficacy and safety of Remdesivir in COVID-19 caused by SARS-CoV-2: A systematic review and meta-analysis

ABSTRACT

Objectives: Evaluation of remdesivir, an RNA polymerase inhibitor, for effectiveness in adults with COVID-19.

Data sources: Electronic search for eligible articles of PubMed, Cochrane Central and clinicaltrials.gov was performed on 20th September, 2020.

Participants & study eligibility criteria: Only RCTs evaluating efficacy of remdesivir in COVID-19 were included for meta-analysis.

Interventions: Remdesivir was compared with standard of care

Primary and secondary outcomes: Primary outcome was mortality and secondary outcomes were time to clinical improvement and safety outcomes like serious adverse events, respiratory failure.

Study appraisal and synthesis methods: Data synthesis was done with Cochrane review manager 5 (RevMan) version 5.3. Cochrane risk of bias 2.0 tool was used for methodological quality assessment. The GRADE pro GDT was applied for overall quality of evidence.

Results: 52 RCTs were screened and 4 studies were included in analysis, with total of 7324 patients. No mortality benefit was observed with remdesivir versus control group[OR=0.92 (95%CI = 0.79 – 1.07), p=0.30, moderate quality evidence]. Significantly higher rates of clinical improvement [OR=1.52 (95%CI = 1.24 – 1.87), p<0.0001, low quality] and faster time to clinical improvement [HR=1.28 (95%CI = 1.12 – 1.46), p=0.0002, very low quality] was observed with remdesivir versus control group. Significant decrease was found in the risk of serious adverse events[RR=0.75 (95%CI = 0.62 – 0.90), p=0.0003, low quality], however no

difference was found in the risk of respiratory failure [RR=0.85 (95%CI = 0.41 – 1.77), p=0.67, very low quality evidence] with remdesivir.

Conclusions: As per the evidence from current review, remdesivir has shown no mortality benefit (moderate quality evidence) in the treatment of COVID-19. From a cost benefit perspective, it is our personal opinion that it should not be recommended for use, especially in low and lower-middle income countries.

Registration: PROSPERO registration number: CRD42020189517

Keywords: Remdesivir, COVID-19, SARS-CoV-2

Article Summary

Strengths and Limitations of this study

- Four RCTs were included in our analysis with total sample size of 7324 patients.
- Risk of bias of RCTs was done using Cochrane ROB-2 scale.
- ROB-2 showed low ROB for WHO Solidarity trial and Wang et al. and high ROB for Beigel et al. and Spinner et al.
- GRADE was applied and overall evidence suggested no mortality benefit with remdesivir (moderate quality evidence).
- Cost-benefit analysis revealed higher cost with no mortality benefit.

INTRODUCTION

Coronavirus disease of 2019 (COVID-19), has created a pandemic all over the world [1, 2]. The global pandemic of SARS-CoV-2 infections has affected more than 141 million people world-wide and has been the cause of 3.026 million deaths globally by 18th of April 2021 as per COVID-19 statistics data. Around 120 million people have recovered and as the trend suggests most of them stay asymptomatic and few of them develop pneumonia like symptoms that does not require oxygen support [3]. A very small percentage get critical to the limit of hypoxia, acute respiratory distress syndrome and multi- organ failure. Among these critical patients who are being put on mechanical ventilation, half of them die.

The search for an effective therapy or preventive modality has become the utmost need of the hour. There are few proposed and approved drugs with some antiviral action and they are under investigation simultaneously across the globe. But as yet no proven effective therapy for SARS -CoV-2 has been accepted widely. Amongst the few promising therapies available remdesivir, a viral RNA polymerase inhibitor has been recommended by US FDA as a drug for compassionate use for treatment of COVID-19 patients. Remdesivir, a nucleoside analogue prodrug, has shown inhibitory effects on SARS-CoV-2, both in vitro and in animal models. However even for the above mentioned studies, contrasting results have been reported in different nations like China and USA [3]. Varied study designs [4, 5], genetic reasons and different treatment regimens (5 or 10 days) have been attributed for this difference.

Only two randomized controlled trials (RCT) have shown efficacy of remdesivir in COVID-19 patients. Many RCTs are undergoing to assess the benefit-risk ratio of remdesivir. Current review was planned to assess the mortality and clinical benefit in addition to safety of remdesivir in the treatment of COVID-19 caused by SARS-CoV-2.

METHODS

Protocol and registration

Review was done following the "PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses") statement. "PROSPERO (International Prospective Register of Systematic Reviews) database" registration was done with study number as CRD42020189517.

Inclusion criteria

Exclusively RCTs evaluating role of remdesivir compared to standard care in COVID-19 were included. Observational studies, review articles, case reports or case series were excluded.

Search and selection of studies

Electronic literature search was performed in PubMed, Cochrane Central Register of Controlled Trials, in addition to clinicaltrials.gov on 20th September 2020, to identify the relevant published articles. Additional Search was done in November 2020 for results of completed trials. Bibliographic search of published articles were also done manually to identify more studies. Only English language studies published were included. Search was performed using medical headings like 'SARS-CoV-2', 'COVID-19', 'Remdesivir', 'COVID', 'novel coronavirus'. RCT restriction was applied. PubMed search strategy is given in Supplementary file 1.

After removal of duplicate articles, two independent authors reviewed the studies for inclusion in review.

Data extraction

Study design, remdesivir doses and regimens, total subjects along with their characteristics, efficacy and safety outcomes were extracted and filled on a pre-structured form.

Study Objectives

The primary objective of review was assessment of mortality (defined as deaths in each group). The secondary outcomes were clinical improvement and virological cure. In addition, serious adverse events and other safety parameters were assessed. Cost-benefit analysis was also performed for remdesivir.

Quality assessment

Two authors independently (DK and AC) performed risk of bias (ROB) of RCTs using Cochrane Collaboration ROB-2 [6]. Overall assessment was recorded as high, low and some concerns. Synthesis of ROB plots was done using online software Robvis (visualization tool)[7].

For publication bias assessment, funnel plot asymmetry was not assessed as studies were less than five. However, Egger's regression test was applied.

Data synthesis and summary measures

Mortality and other outcome data were presented as odd ratios (OR) or Hazard ratio (HR) with 95% confidence intervals (CI). Synthesis of data was done using "Review Manager 5 (RevMan) Version 5.3" (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014)[8]. The heterogeneity among RCTs included in review was judged with I^2[9, 10]. The results of both fixed and random effect model were assessed for interpretation [9, 11].

Quality of Evidence - GRADE Pro GDT

GRADE pro GDT (guideline development tool) software (https://gradepro.org/.) was applied for assessment of overall quality of evidence.[12] Optimal information size (OIS) or sample

size for either group was computed to be 1213 patients. Overall GRADE assessment was classified as high, moderate, low or very low [12].

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study PRISMA flow diagram

The RCTs included in review are depicted in PRISMA flow chart (Figure 1). Out of total 52 records screened, 4 RCTs [3,13-15] were included in analysis. One study was excluded as it was single arm study [4], one was in Spanish language and other two were non-COVID trial [16] and historical control study [17].

Study characteristics

Study characteristics of RCTs of present systematic review are mentioned in Table 1.

Risk of bias (ROB)

The overall ROB was judged as "Low", as ROB for WHO solidarity trial[14] and Wang et al.[3] was assessed as low. Study done by Beigel et al.[13] and Spinner et al.[15] was regarded as having "High" ROB. Hence, ROB assessed for outcomes having data only from Beigel et al. and Spinner et al. in GRADE analysis was regarded as having serious issues. The ROB of RCTs is represented in Figure 2 and Supplementary Figure 1.

Efficacy outcomes

Mortality

Mortality data was included from 4 RCTs with 3818 and 3506 patients in remdesivir and standard of care groups, respectively. Remdesivir was found to have no mortality benefit as compared to control group [OR=0.92 (95%CI = 0.79 – 1.07), p=0.30; I^2=0] (Figure 3a). Sub-

group analysis revealed no mortality benefit in low risk and high risk groups (Figure 3a, Supplementary Figure 2)

Clinical Improvement

Statistically significant increase in rates of clinical improvement in remdesivir versus controls was observed [OR=1.52 (95%CI = 1.24 – 1.87), p<0.0001; I^2=0%] (Figure 3b). Results were drawn from 3 RCTs with total of 1879 patients.

Time to clinical improvement

Pooled analysis revealed that there was significantly faster time to clinical improvement in remdesivir group as compared to controls [HR=1.28 (95%CI = 1.12 – 1.46), p=0.0002; I^2=0%](Figure 3c). Data extracted from 2 RCTs with total of 1292 patients.

Safety outcomes

Serious Adverse Events (AE)

Pooled analysis revealed significant decrease in the risk of serious adverse events in remdesivir group as compared to control [RR=0.75 (95%CI = 0.62 – 0.90), p=0.0003; I^2=0%] (Figure 4a). This data was extracted from 3 RCTs with a total of 1875 patients.

Respiratory Failure

No difference in the risk of respiratory failure between remdesivir and control groups was found [RR=0.85 (95%CI = 0.41 – 1.77), p=0.67; I^2=55%] (Figure 4b). Findings were derived from 2 RCTs with a total of 1291 patients.

Cost-benefit analysis

The cost of remdeisvir is US $ 2340 per patient. There is lack of mortality benefit as per our review.

Publication bias

Though the funnel plot asymmetry was not assessed, the Egger's regression test applied on four studies included in mortality rate assessment showed no publication bias (t = - 0.5947, p = 0.6123).

GRADE analysis of the primary and secondary outcomes (Table 2)

The GRADE analysis recommendation for mortality was 'Moderate' evidence quality. Though there is low ROB, low heterogeneity and direct outcome but there are serious concerns with imprecision. The quality of evidence for clinical improvement and time to clinical improvement were graded as "Low" and "Very Low" respectively. The GRADE recommendation for serious AE and respiratory failure were "Low" and "Very low" quality of evidence respectively, as there was presence of high ROB and high imprecision. The GRADE recommendation is shown in table 2.

Discussion

With the existing recommendation of USFDA for compassionate use of Remdesivir in COVID patients, it is being used worldwide. Current systematic review was planned for formulating recommendation from RCTs evaluating the efficacy of remdesivir in COVID-19 patients.

In the current systematic review, the OR for mortality failed to show any significant mortality benefit with the use of remdesivir. WHO solidarity trial[14] showed no mortality benefit with the use of remdesivir. Though it was an open label study, it is less likely to have bias in assessment of objective outcome like mortality. A total of 3451 patients were included in remdesivir and standard of care groups. Subgroup analysis revealed no mortality benefit in low risk (Figure 3a - no oxygen requirement, Supplementary Figure 2 – No invasive ventilation) or

high risk (Figure 3a - oxygen requirement or assisted ventilation, Supplementary Figure 2 – Invasive ventilation) group of patients with remdesivir.

At the time of recruitment, more patients were on invasive mechanical ventilation or ECMO in the placebo group. There were significantly more adverse events reported in the control group in our review. This was due to the high incidence of serious AE in Beigel et al study.[13] This is rare occurrence that serious AE were significantly more in control group. The fact that more severe patients were randomized into control group in the study by Beigel et al.[13] is the major reason for this finding. Similarly, the serious AE which also included the clinical events like renal failure and respiratory failure (5.2% in remdesivir and 8% in placebo arm) were also observed more in placebo group. Despite this imbalance, remdesivir was unable to show superiority in mortality rate.

Sub-group analysis of Beigel et al.[13] study revealed that remdesivir resulted in significant rate of clinical improvement in COVID-19 patients on oxygen therapy, while the patients not on oxygen, or on high flow oxygen or non-invasive ventilation and receiving mechanical ventilation or ECMO had similar clinical improvement as standard of care.

Placebo used in Beigel et al.[13] study was sulfo-butyl-ether b-cyclodextrin-sodium (SBECD), used to dissolve remdesivir. The maximum recommended daily dose is approximately 250 mg/kg solvent used to dissolve remdesivir.[13] The amount of solvent present in placebo was not quantified in protocol. Dose of solvent should be modified in patients with eGFR fall of more than 50% from baseline and is contraindicated in patients with eGFR less than 30ml/min. But such modification were not done in either arms. Hence the effect of solvent on patients with impaired renal function can be detrimental and cannot be ruled out.

In the study by Beigel et al.[13], the median time of administration of drug from randomization was nine days. Median recovery time from randomization was 11 days. In addition, 302 patients in remdesivir group did not receive 10 days of treatment. Therefore, it is difficult to infer that remdesivir resulted in recovery of patients, as an average of 2 days of administration of remdesivir resulting in complete recovery of patients seems implausible.

Virological cure is also an important outcome which was neglected by the authors. Wang et al. reported no difference (percentage difference = -7.5 (95% CI = -19.2 to 4.2)) in undetectable viral RNA load in remdesivir (75.6%) and placebo groups (83.1%). Patients may become asymptomatic but not cured. It has been observed that asymptomatic patients with RT-PCR positive test can have thromboembolic and chest CT changes. Study done by Merkler et al. observed that eight patients (26%) out of total 31 ischemic stroke patients were COVID-19 positive on RT-PCR testing. They didn't have any COVID-19 symptoms on presentation [18]. Silent hypoxemia is a disturbing feature in asymptomatic COVID patients and has been found to be associated with poor outcomes [19].

The SIMPLE trial [4] results published in New England Journal of Medicine does not include a standard of care group. Similar to Beigel et al. virological cure was not reported[4]. Clinical status at day 14 was similar in 5 day course of remdesivir as compared to 10 day course. However, in comparison to standard care, 5 day group (OR 1.65 [95% CI 1.09-2.48]; p=0.017) showed significant improvement while 10 day group did not (OR 1.31 [95% CI 0.88-1.95]; p=0.18). Death reported on day 11 was similar in all three groups[20].

In another study published by Grein et al.[5] in which compassionate use of remdesivir was done, did not have a control arm. Hence, the conclusion that remdesivir is effective cannot be drawn as the possibility of observing similar findings in control arm cannot be ruled out.

Three systematic reviews and meta-analysis were published on remdesivir[21-23]. However, none of the reviews have included WHO solidarity trials in review. Exclusion of such large study (N=3451) decreases the power of systematic reviews. Our results are different from all three systematic reviews as Wilt et al.[23] and Shrestha et al.[21] have concluded mortality benefit with remdesivir while Elsawah et al.[22] concluded significant clinical improvement with remdesivir as compared to standard care. Meta-analysis performed by Solidarity trial group[14] has shown no mortality benefit (OR=0.91, 95% CI = 0.79-1.05), similar to our review. They did not perform meta-analysis with regard to other clinical endpoints and safety outcomes. Also, ROB-2 analysis of included RCTs and GRADE analysis was not applied.

The cost of the drug is $2340 per patient but with no mortality benefit[24]. According to World Bank data, low and lower-middle income countries have Gross National Income (GNI) per capita less than or equal to $ 1035 and between $ 1036 to $ 4045, respectively.[25] As per World Health Organization Global Health Expenditure database (2018), current health expenditure per capita in low and lower-middle income countries is less than $36 and $ 86, respectively.[26] Therefore, from a cost benefit perspective, we are of the opinion that their use should not be recommended, especially in low and lower-middle income countries. In case of limited use, strict evidence based guidelines should be followed for optimum health benefits. The cost of the drug will put extra burden on government by increasing the health cost without any benefit. Injudicious use of remdesivir without mortality benefit may also lead to increased incidence of adverse events.

Limitations and strengths

A major strength of our systematic review is that four RCTs were included in our analysis with total sample size of 7324 patients. Study done by Wang et al and WHO Solidarity trial has low

ROB. Robust method of analysis using ROB-2 and GRADE analysis is another strength of the current systematic review.

Quality of Evidence: (GRADE)

The overall quality of systematic review is "Moderate". Critical outcomes like mortality has moderate quality evidence. Clinical improvement was regarded as "Low". Time to clinical improvement has "Very low" quality of evidence. Time to clinical improvement was used by regulatory agencies like US FDA for giving approval to remdesivir for treatment of severe COVID-19 patients. However, the quality of evidence for time to clinical improvement cannot be overlooked. This evidence suggests that further research is very likely to have an important impact on our confidence in the estimate of time to clinical improvement and likely to change the estimate. Moderate quality of evidence with regard to mortality showed that further RCTs are likely to have important impact and may change the no mortality benefit conclusion drawn from review.

Conclusion:

Evidence of our systematic review indicates no benefit in mortality rate with remdesivir, with moderate quality of evidence. Benefit does exist in terms of rates of clinical improvement and faster time to clinical improvement in favour of remdesivir, but the evidence is of low and very low quality, respectively. Significant decrease in serious adverse events as compared to placebo, strengthens the evidence of more serious patients in placebo arm. No difference was shown in respiratory failure in the two groups (very low quality evidence). All outcomes except mortality in our meta-analysis were influenced by Beigel et al. and Spinner et al., which has high ROB. WHO solidarity trial and Wang et al showed no mortality benefit, both having overall low ROB.

Abbreviation List

COVID-Corona Virus Disease

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - International Prospective Register of Systematic Reviews

ROB-2 - The Risk of Bias -2 tool for randomized control trials

CI: Confidence interval

OR - Odd ratios

HR - Hazard ratios

GRADE pro GDT - Grades of Recommendations, Assessment, Development and Evaluations (GRADE) guideline development tool

OIS - Optimal information size

Declarations

Ethical approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of supporting Data: The datasets used and/or analyzed during the current study are available from the corresponding author on request

Competing Interests: Dr. SINGH has nothing to disclose. Dr. CHUGH A has nothing to disclose. Dr Khera D has nothing to disclose. Dr Khera P has nothing to disclose. Dr. CHUGH V has nothing to disclose.

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Authors Contribution:

Study design and planning of systematic review - All of the authors

Literature search - AC, SS, PSK

Figures – SS, VKC, AC

Tables - DK, SS

Data collection and analysis - SS, DK

ROB - DK, AC, SS, Query resolved by all authors

GRADE Analysis - SS, AC, DK, Query resolved by all authors

Data interpretation -, SS, DK, AC

Writing - SS, DK, AC, PSK

Corrections and Final approval of Manuscript - All of the authors

The corresponding author attests that all listed authors meet authorship criteria as per ICJME and that the manuscript is an honest, accurate, and transparent account of the study being reported

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Table 1. Characteristics of clinical studies evaluating Remdesivir for treatment of COVID-19

Author, year (Study design)	Institution/ Country of study conduct	Study Interventions (N)/ Regimen	Study control (N)/ Regimen	Study population characteristics	Study outcomes
Beigel et al 2020 (Randomized controlled trial)	Multicenter trial	Remdesivir (538); 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	Placebo (521)	Hospitalized adults COVID-19 patients with evidence of lower respiratory tract involvement.	**Time to recovery:** Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% confidence interval [CI], 1.12 to 1.55; P<0.001 **Mortality:** Kaplan Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04)
Spinner et al (Randomized controlled trial)	Multicenter trial	Remdesivir - 10-day (n = 197), Remdesivir - 5-day (n = 199)	Standard care (n = 200)	Confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%)	**Day 28** Mortality rate n(%) – Remdesivir 10 day = 3(2); Remdesivir 5 day = 2(1), Standard = 4(2) Clinical Improvement n(%) - Remdesivir 10 day =174((90), Remdesivir 5 day = 171(90), Standard = 166(83)
Wang et al 2020 (Randomized controlled trial)	Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital,	Remdesivir (158); at least 1 dose after entering ICU; 200 mg on day 1 followed by 100 mg on days 2–10 in	Placebo (79)	Hospitalized adults COVID-19 patients with symptom onset to enrolment interval of ≤ 12 days, oxygen saturation ≤ 94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300	**Time to clinical improvement within 28 days after randomization:** Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]

	Beijing, China	single daily infusions		mm Hg or less, and radiologically confirmed pneumonia	**28-day mortality:** similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI –8·1 to 10·3]).
WHO Solidarity Trial 2020 (Randomized controlled trial)	World Health Organization, Multicentric trial (405 hospitals in 30 countries)	Remdesivir (2743); Day 0, 200mg; days 1-9, 100mg	Placebo (2708)	Hospitalized with a diagnosis of COVID-19, age ≥18 years, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours	**Mortality rate:** Remdesivir RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control). Hydroxychloroquine RR=1.19 (0.89-1.59, p=0.23; 104/947 vs 84/906), Lopinavir RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372) Interferon RR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050)

Table 2: GRADE recommendation for primary and secondary outcomes of use of Remdesivir in COVID-19

Certainty assessment						№ of patients		Effect		Certainty Importance
№ of studies Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Efficacy and Safety of Remdesivir**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Mortality at day 28										
4 RCT	not serious [a]	not serious	not serious	serious [b]	none	387/3818 (10.1%)	394/3506 (11.2%)	**OR 0.92** (0.79 to 1.07)	**8 fewer per 1,000** (from 21 fewer to 7 more)	⊕⊕⊕◯ MODERATE CRITICAL
Clinical Improvement										
3 RCT	serious [c]	not serious	not serious	serious [d]	none	782/1080 (72.4%)	484/799 (60.6%)	**OR 1.52** (1.24 to 1.87)	**94 more per 1,000** (from 50 more to 136 more)	⊕⊕◯◯ LOW IMPORTANT
Time to clinical Improvement										
2 RCT	serious [e]	not serious	serious [f]	serious [d]	none	-/0	-/0	**HR 1.28** (1.12 to 1.46)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕◯◯◯ VERY LOW IMPORTANT
Serious Adverse events										
3 RCT	serious [c]	not serious	not serious	serious [d]	none	161/1075 (15.0%)	179/800 (22.4%)	**RR 0.75** (0.62 to 0.90)	**56 fewer per 1,000** (from 85 fewer to 22 fewer)	⊕⊕◯◯ LOW IMPORTANT
Respiratory Failure										
2 RCT	serious [e]	serious [g]	not serious	serious [h]	none	44/691 (6.4%)	48/600 (8.0%)	**RR 0.85** (0.41 to 1.77)	**12 fewer per 1,000** (from 47 fewer to 62 more)	⊕◯◯◯ VERY LOW CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio; **RR:** Risk ratio; RCT – Randomized controlled trials

Explanations

a. All studies have low ROB except Biegel and Spinner et al. WHO solidarity trial contributing 77.9% weight to overall effect has low ROB. Hence overall low ROB.

b. Overall information size of 1213 was achieved in either group. However, the overall effect estimate included one, hence downgraded for imprecision.

c. Biegel et al. and Spinner et al. have a high risk of bias (ROB) due to selective reporting of results. Hence, downgraded for ROB.

d. Overall Information Size of 1213 was not achieved in either groups. Hence, downgraded for imprecision.

e. Biegel et al. has a high risk of bias (ROB) due to selective reporting of results. Hence, downgraded for ROB.

f. Time to clinical improvement is not a direct estimate of the patient's oriented outcomes. Hence, downgraded for evidence.

g. As I^2 >50%, heterogeneity is significantly high. Hence, downgraded for inconsistency

h. Overall information size of 1213 was not achieved in either group and the overall effect estimate included one, hence downgraded for imprecision.

Captions for Figures

Figure 1: PRISMA flow chart depicting study selection process

Figure 2: ROB-2: Risk of bias in RCT evaluating Remdesivir for treatment of COVID-19

Figure 3: Mortality rate (3a), clinical improvement (3b) and time to clinical improvement (3c) of remdesivir vs control treatment

Figure 4: Number of patients with Serious adverse events (4a) and respiratory failure (4b) (remdesivir vs control treatment)

Supplementary Figure 1: ROB-2: Risk of bias of RCT evaluating remdesivir in COVID-19 (Weighted Summary plot)

Supplementary Figure 2: Forest plot of mortality rates in low risk (with or without O2) versus high risk (Invasive ventilation) Groups for use of remdesivir versus standard of care in COVID-19

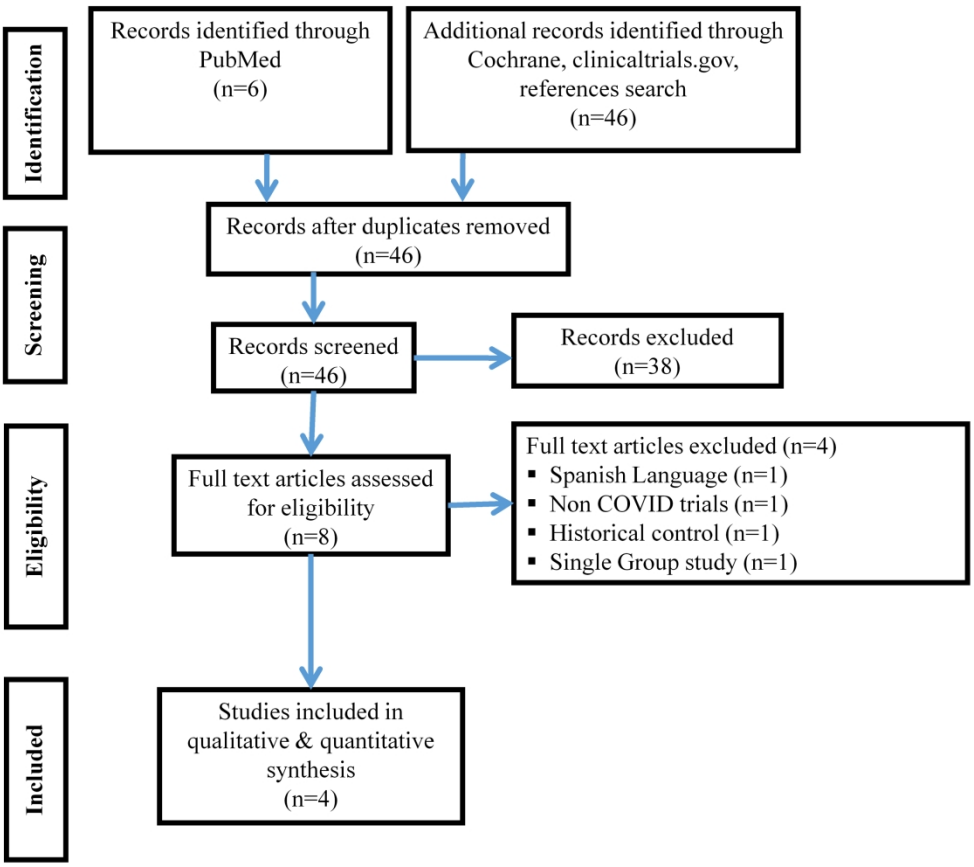

Figure 1: PRISMA flow chart depicting study selection process

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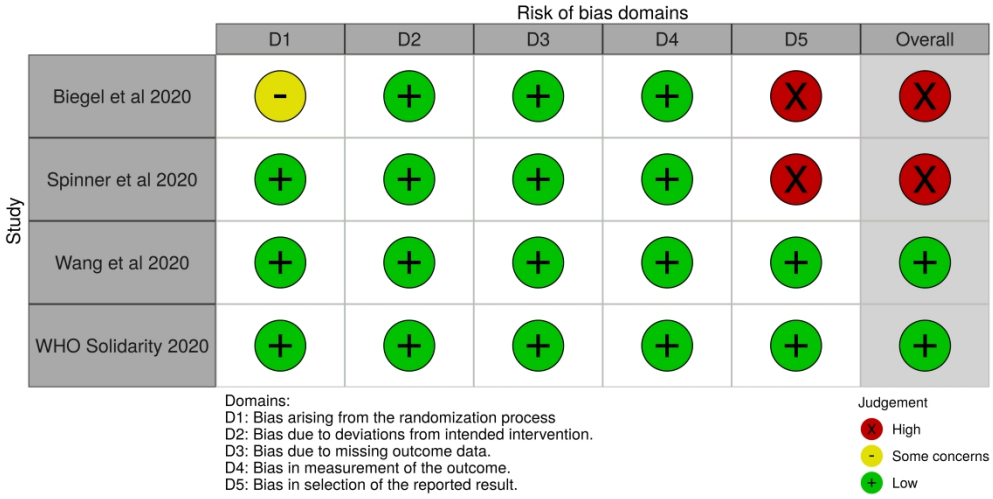

Figure 2: ROB-2: Risk of bias in RCT evaluating Remdesivir for treatment of COVID-19

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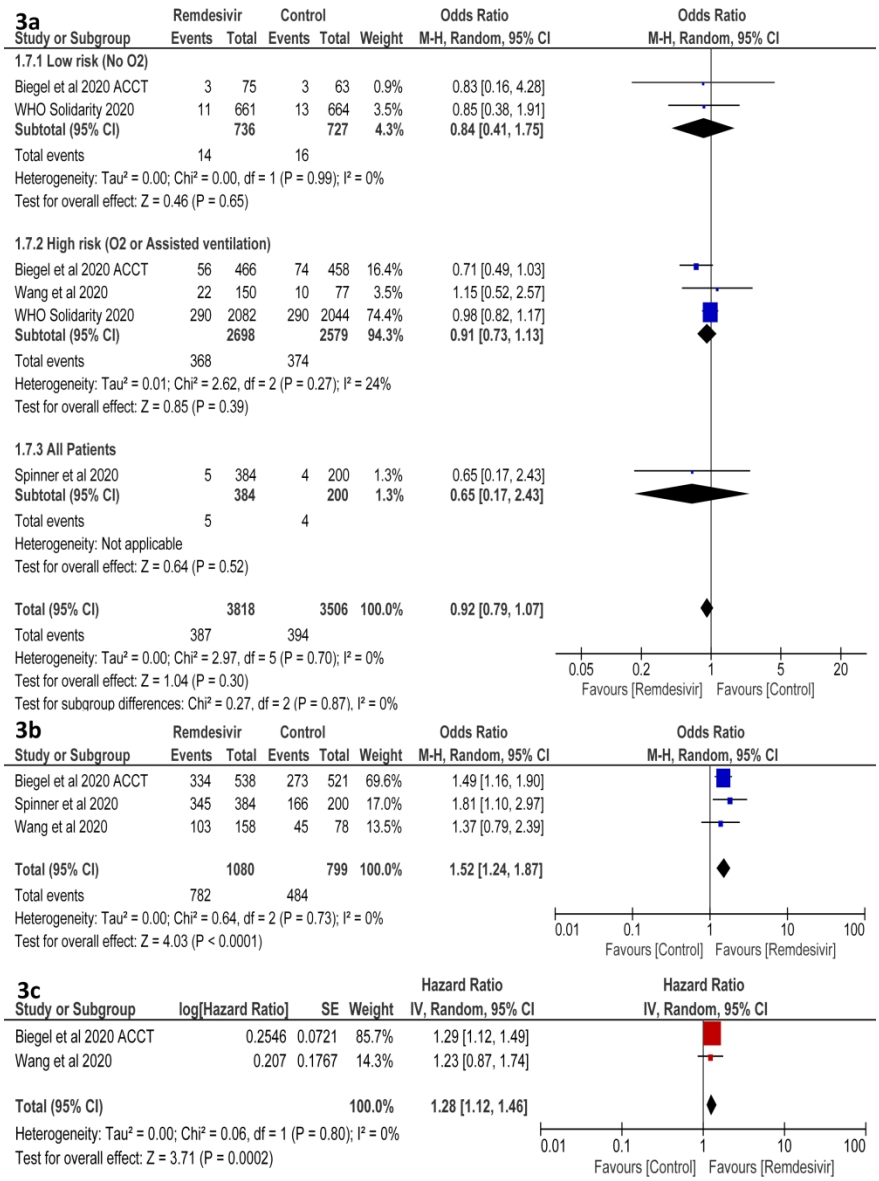

Figure 3: Mortality rate (3a), clinical improvement (3b) and time to clinical improvement (3c) of remdesivir vs control treatment

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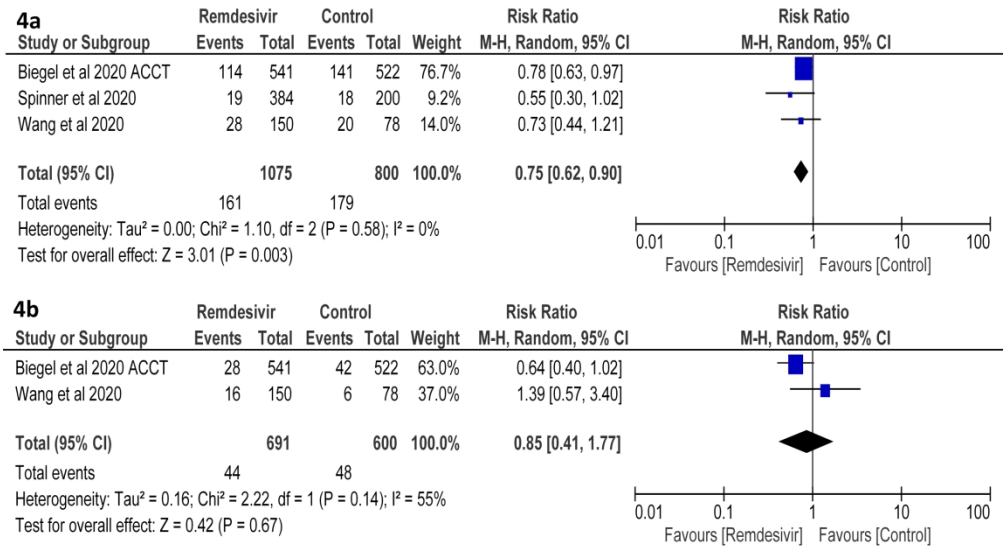

Figure 4: Number of patients with Serious adverse events (4a) and respiratory failure (4b) (remdesivir vs control treatment)

158x89mm (400 x 400 DPI)

Search Strategy for PubMed

Search number	Query	Filters	Search Details
6	((SARS-CoV-2) OR (COVID-19)) AND (Remdesivir)	Clinical Trial, Randomized Controlled Trial	(("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])))) AND ("remdesivir"[Supplementary Concept] OR "remdesivir"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])
5	((SARS-CoV-2) OR (COVID-19)) AND (Remdesivir)	Clinical Trial	(("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])))) AND ("remdesivir"[Supplementary Concept] OR "remdesivir"[All Fields])) AND (clinicaltrial[Filter])

4	((SARS-CoV-2) OR (COVID-19)) AND (Remdesivir)		("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND ("remdesivir"[Supplementary Concept] OR "remdesivir"[All Fields])
3	SARS-CoV-2		"sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields]
2	COVID-19		"covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])
1	Remdesivir		"remdesivir"[Supplementary Concept] OR "remdesivir"[All Fields]

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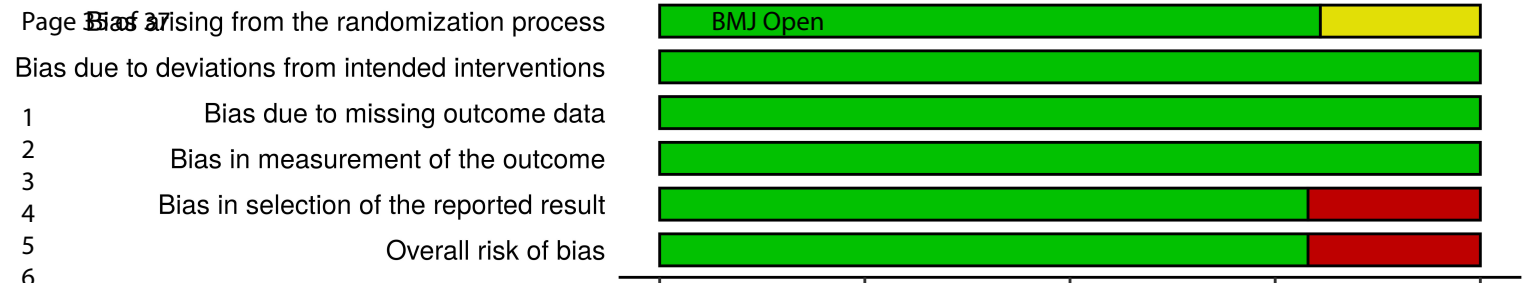
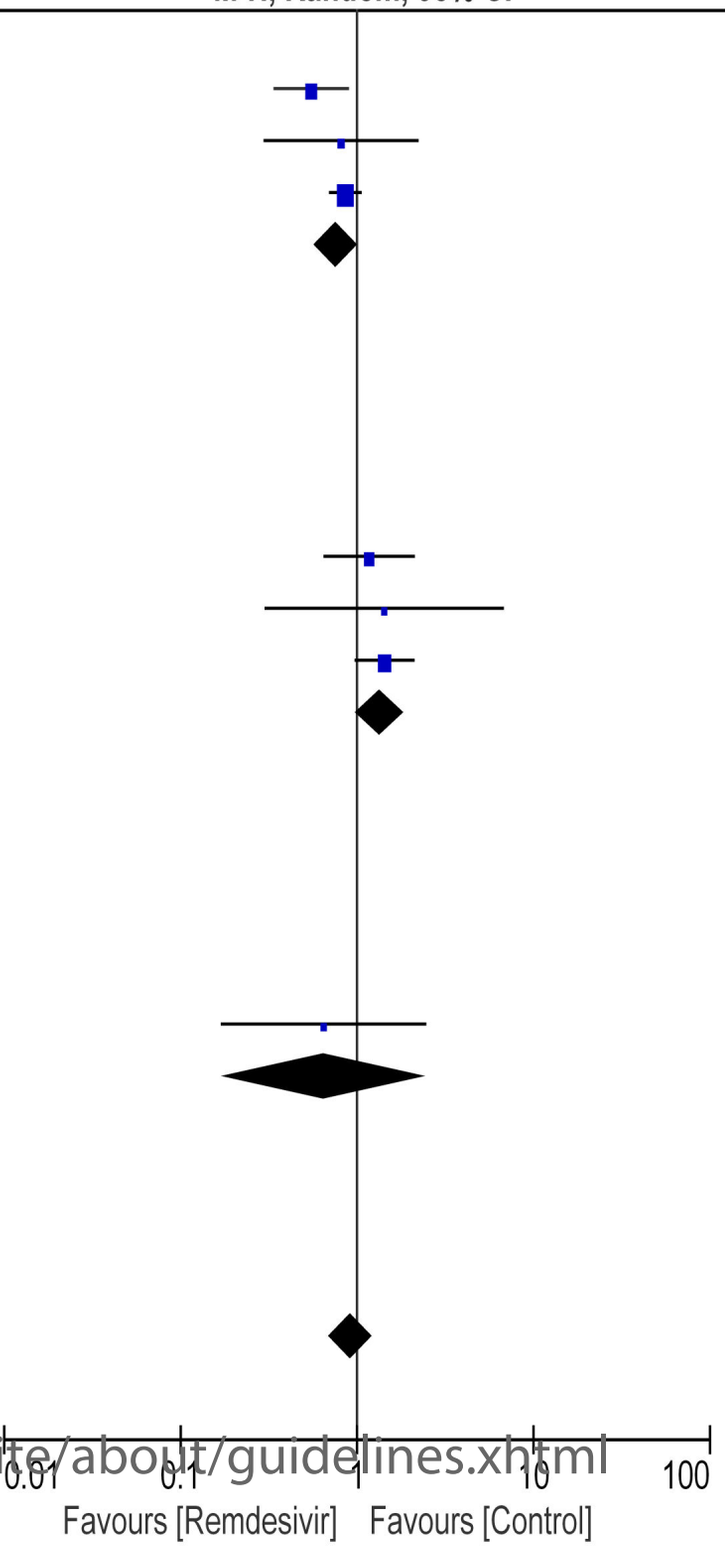
Supplementary Figure 1: ROB-2: Risk of bias of RCT evaluating remdesivir in COVID-19 (Weighted Summary plot)



Supplementary Figure 2: Forest plot of mortality rates in low risk (with or without O2) versus high risk (Invasive ventilation) Groups for use of remdesivir versus standard of care in COVID-19

Study or Subgroup	Remdesivir Events	Remdesivir Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.8.1 Low risk (O2 but no Invasive ventilation)						
Biegel et al 2020 ACCT	31	402	48	364	18.1%	0.55 [0.34, 0.89]
Wang et al 2020	11	129	7	68	6.7%	0.81 [0.30, 2.20]
WHO Solidarity 2020	203	2489	232	2475	30.9%	0.86 [0.70, 1.05]
Subtotal (95% CI)		**3020**		**2907**	**55.8%**	**0.76 [0.56, 1.02]**
Total events	245		287			
Heterogeneity: Tau² = 0.02; Chi² = 2.87, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 1.85 (P = 0.06)						
1.8.2 High Risk (Invasive ventilation)						
Biegel et al 2020 ACCT	28	131	29	154	14.6%	1.17 [0.66, 2.10]
Wang et al 2020	11	29	3	10	3.1%	1.43 [0.30, 6.70]
WHO Solidarity 2020	98	254	71	233	22.3%	1.43 [0.98, 2.09]
Subtotal (95% CI)		**414**		**397**	**40.0%**	**1.35 [0.99, 1.84]**
Total events	137		103			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.06)						
1.8.3 All Patients						
Spinner et al 2020	5	384	4	200	4.1%	0.65 [0.17, 2.43]
Subtotal (95% CI)		**384**		**200**	**4.1%**	**0.65 [0.17, 2.43]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**3818**		**3504**	**100.0%**	**0.93 [0.70, 1.24]**
Total events	387		394			
Heterogeneity: Tau² = 0.06; Chi² = 11.59, df = 6 (P = 0.07); I² = 48%						
Test for overall effect: Z = 0.50 (P = 0.62)						
Test for subgroup differences: Chi² = 7.48, df = 2 (P = 0.02), I² = 73.3%						



*In ventilation subgroup, Wang et al study included patients on high flow oxygen in addition to invasive ventilation

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12, 4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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