PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of Remdesivir in COVID-19 caused by SARS-CoV-2: A systematic review and meta-analysis
AUTHORS	Singh, Surjit; Khera, Daisy; Chugh, Ankita; Khera, Pushpinder; Chugh, Vinay

VERSION 1 – REVIEW

REVIEWER	Gkrania-Klotsas, Effrossyni Cambridge University Hospitals NHS Foundation Trust, Department of Infectious Diseases
REVIEW RETURNED	06-Feb-2021

GENERAL COMMENTS	This is an excellent and timely systematic review, prepared in a very clear way. Two small changes would make this paper ready for publication 1. The abstract suggests a formal cost benefit analysis has been performed while the text makes it clear it has not (“ 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”). Please revise the abstract to reflect that this is a personal opinion 2. As per the checklist, a full copy of your MeSH strategy (not just the terms) has to be included in the paper. Please include. 3. Please state the criteria used to exclude papers as per figure 1 in the screening page more clearly and reference the 38 records excluded in a supplementary file. 4. There is a significant overlap between this study and the paper (referenced) by Pan etc 2020 (SOLIDARITY). In the latter paper, a similar meta analysis is included. Please explain clearly what the added value of your work is in this context and make it clear in the text that this overlap exists. Comment and compare to Pan et al metanalysis in terms of differences in results.

REVIEWER	Ferner, Robin West Midlands Centre for Adverse Dr.ug Reactions
REVIEW RETURNED	07-Feb-2021

GENERAL COMMENTS	Efficacy and safety of Remdesivir in COVID-19 The BMJ Living Systematic Review (Siemieniuk) covers the same ground, but this is from the prospect of a developing country. However, you do not any detail about the view that 'remdesivir should not be used 'especially in lower to middle income countries.' This is important, because otherwise your review adds little to Siemieniuk's. Only RCTs evaluating role of remdesivir compared to standard care in COVID-19 were included.

	Your analysis therefor differs from Siemieniuk's by omitting Goldman's SIMPLE trial of 5 -v- 20 days of remdesivir—mentioned later in your review. Page 10/33 Line 24: Four trials (Beigel, Pan, Spinner, and Wang) but only three citations. Page 10/33 Line 60: The Odds Ratio for mortality closely approaches the OR found by the earlier systematic reviewers using Bayesian methods—0.90, credible interval 0.70–1.12, which is encouraging. Page 11/33 Line 31: The sentence '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; I2=0%]' is inverted. Page 14/33 Line 3: You say: 'The virological cure is the most important outcome which was neglected by the authors.' Surely, clinical cure is the most important outcome? Minor comments The manuscript is generally clear. You sometimes omit definite or indefinite articles. Page 11/33 Line 49: 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 → Though the funnel plot asymmetry was not assessed, the Egger's regression test applied on four studies included in the mortality rate assessment showed no publication bias. Page 12 Line 27: Please explain and rephrase: 'Current systematic review was planned for recommendation drawn from RCTs evaluating the efficacy of remdesivir in COVID-19 patients.' Page 12/33 Line 37: In the current systematic review, ORs for mortality was unable to confer any mortality benefit with the use of remdesivir → In the current systematic review, the OR for mortality failed to show any significant mortality benefit with the use of remdesivir. Page 12/33 Line 59: There were significantly more number of serious adverse events reported in our review due to increase serious AE in Beigel et al study → There were significantly more adverse events reported in the control group in our review . This was due to the increase serious AE in Beigel et al study. Page 15/33 Line 19: GARDE → GRADE

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Thank you Dr. Effrossyni Gkrania for your valuable comments and suggestions.

Dr. Effrossyni Gkrania - Klotsas, University of Cambridge
Comments to the Author:
This is an excellent and timely systematic review, prepared in a very clear way. Two small changes would make this paper ready for publication 1. The abstract suggests a formal cost benefit analysis has been performed while the text makes it clear it has not ("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"). Please revise the abstract to reflect that this is a personal opinion
Answer: We have revise the abstract as asked by you. The line has been rephrased to "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 developing countries."
In addition the cost benefit assessment has been added to methodology and result section including discussion on low and lower-middle income countries – Page 15.

2. As per the checklist, a full copy of your MeSH strategy (not just the terms) has to be included in the paper. Please include.
Answer: Full copy of MeSH strategy is included in Supplementary file 1. It has been included in manuscript file.

3. Please state the criteria used to exclude papers as per figure 1 in the screening page more clearly and reference the 38 records excluded in a supplementary file.
Answer: Stated the criteria in screening page of article – Page 10 result section. All 38 references are added in supplementary file.

4. There is a significant overlap between this study and the paper (referenced) by Pan etc 2020 (SOLIDARITY). In the latter paper, a similar meta analysis is included. Please explain clearly what the added value of your work is in this context and make it clear in the text that this overlap exists. Comment and compare to Pan et al metanalysis in terms of differences in results.
Answer: We have added the comparison. We did a meta-analysis which is similar to Pan et al. In addition we did Risk of bias analysis as well as GRADE analysis which was not done by Pan et al (WHO Solidarity trial). The conclusion with regard to mortality of our review is similar to Pan et al. Cost-benefit analysis was also added in methodology and result section.
I have included the text in manuscript file with comparison to Pan et al in discussion – Page 15.

Reviewer: 2
Thank you Prof. Robin Ferner for your valuable comments and suggestions.

Prof. Robin Ferner, West Midlands Centre for Adverse Dr.ug Reactions
Comments to the Author:
BMJ Open 2020-048416
Efficacy and safety of Remdesivir in COVID-19

The BMJ Living Systematic Review (Siemieniuk) covers the same ground, but this is from the prospect of a developing country. However, you do not any detail about the view that 'remdesivir should not be used 'especially in lower to middle income countries.' This is important, because otherwise your review adds little to Siemieniuk's.
Answer: We have tried to add our view point with regard to remdesivir use in lower to middle income countries. Cost-benefit analysis added in methodology, results and the same has been discussed in dscussion section. Page 15, last paragraph before strength and limitations.

Only RCTs evaluating role of remdesivir compared to standard care in COVID-19 were included.

Your analysis therefor differs from Siemieniuk's by omitting Goldman's SIMPLE trial of 5 -v- 20 days of remdesivir—mentioned later in your review.
Answer: Goldman's SIMPLE trial is single group and therefore excluded from analysis. Secondly different time points were taken for evaluation by Goldman et al. All patients' analysis should have been done at the end of 28 days or till recovery of all patients. The time point analysis can introduce bias, hence the results cannot be relied upon.

Page 10/33 Line 24: Four trials (Beigel, Pan, Spinner, and Wang) but only three citations.
Answer: Corrections done. Thank you

Page 10/33 Line 60: The Odds Ratio for mortality closely approaches the OR found by the earlier systematic reviewers using Bayesian methods—0.90, credible interval 0.70–1.12, which is encouraging.
Answer: Thank you for appreciation

Page 11/33 Line 31: The sentence '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; I2=0%]' is inverted.
Answer: Text modified. Thank you

Page 14/33 Line 3: You say: 'The virological cure is the most important outcome which was neglected by the authors.' Surely, clinical cure is the most important outcome?
Answer: Agreed with you. We have modified the statement to "Virological cure is also an important outcome which was neglected by the authors."
Silent hypoxia and Post-COVID syndrome has been seen in asymptomatic patients. Disease may continue despite the fact that the patient is asymptomatic. We have cited some articles in evidence of above statement in our discussion.

Minor comments
The manuscript is generally clear.
You sometimes omit definite or indefinite articles.

Page 11/33 Line 49: 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 → Though the funnel plot asymmetry was not assessed, the Egger's regression test applied on four studies included in the mortality rate assessment showed no publication bias.
Answer: Done. Thank you

Page 12 Line 27: Please explain and rephrase: 'Current systematic review was planned for recommendation drawn from RCTs evaluating the efficacy of remdesivir in COVID-19 patients.'
Answer: Rephrasing done. Current systematic review was planned for formulating recommendation from RCTs evaluating the efficacy of remdesivir in COVID-19 patients. We mean to say that Evidence from RCT will help in making recommendations.

Page 12/33 Line 37: In the current systematic review, ORs for mortality was unable to confer any mortality benefit with the use of remdesivir → In the current systematic review, the OR for mortality failed to show any significant mortality benefit with the use of remdesivir.
Answer: Done

Page 12/33 Line 59: There were significantly more number of serious adverse events reported in our review due to increase serious AE in Beigel et al study → There were significantly more adverse events reported in the control group in our review . This was due to the increase serious AE in Beigel et al study.
Answer: Done

Page 15/33 Line 19: GARDE → GRADE
Answer: Done