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Supplementary Material

Remdesivir for the Treatment of Severe SARS-CoV-2 (COVID-19): A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Coronavirus Disease in 2019 (COVID-19) is a pandemic caused by SARS-CoV-2 infection. Over 53 million people have been infected with over 1.3 million deaths. However, there is no standard treatment or vaccines to date. Recently, several randomized controlled trials and cohort studies have demonstrated the efficacy of remdesivir for the treatment of severe COVID-19 patients. This is a systematic review and meta-analysis to define its efficacy.

Methods: A systematic review was done on databases (PubMed, Embase, Medline, Cochrane) on 9 Nov 2020. Search keywords were remdesivir, COVID-19, SARS-CoV-2, randomized controlled trials and cohort studies. Studies with high-evidence values were selected to evaluate its clinical efficacy in terms of risk ratio, time to clinical improvement, and mortality risk. Subgroup analysis was performed based on baseline hospitalization status, age and ethnicity.

Results: Of the 1328 studies, 6 studies were selected and pooled for meta-analysis. Remdesivir was associated with clinical improvement (risk ratio 1.14, 95% CI 1.02-1.28, p=0.02). It shortened the mean time of clinical improvement by 3.32 days (95% CI -4.37 to -2.28, p<0.001). However, its use was not associated with reduced mortality risk (risk ratio 0.75, 95% CI 0.40–1.40). In subgroup analysis, remdesivir was associated with clinical improvement in patients without the need of invasive ventilation (risk ratio 1.90, 95% CI 1.58-2.29, p<0.001; hazard ratio 2.22, 95% CI, 1.64-3.02), and age less than 70 years (risk ratio 2.14, 95% CI 1.39-3.28, p<0.001).

Conclusion: Remdesivir is effective in the treatment of severe COVID-19 patients, in particular those without invasive ventilation.

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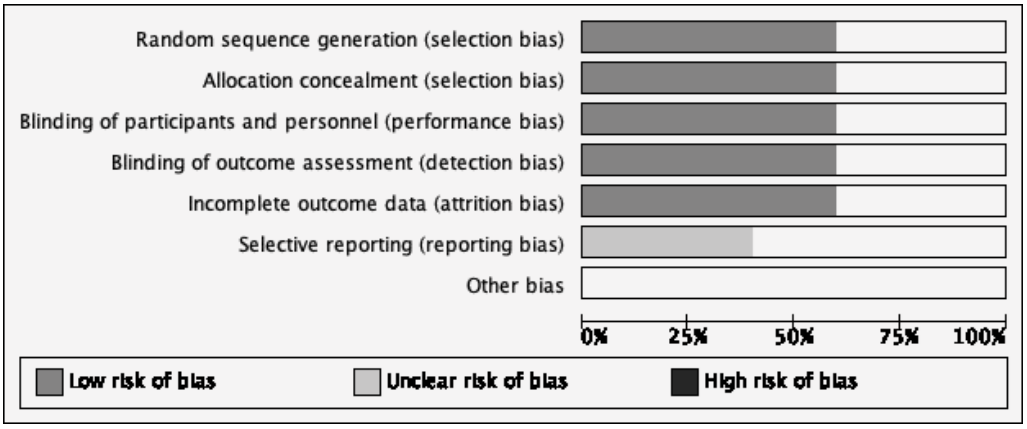
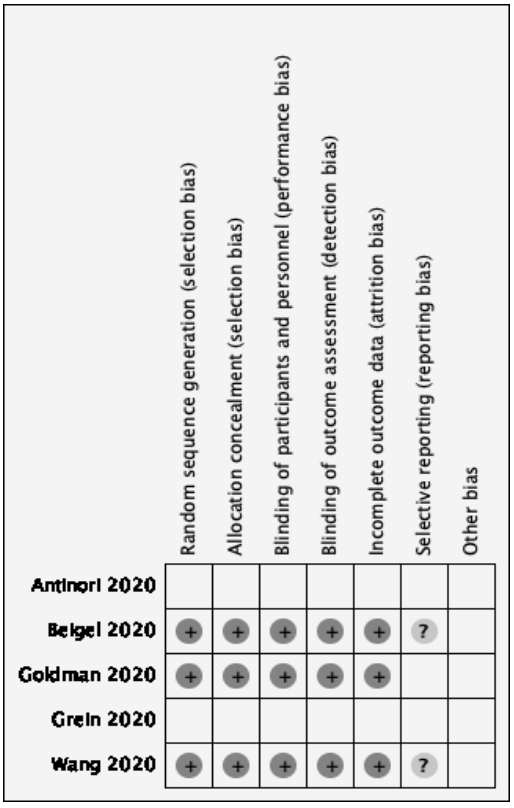
S1: Risk of bias graph.



S2: Risk of bias summary table. The risk of cohort studies (Antonri 2020, and Grein 2020) will be assessed by Newcastle-Ottawa Scale for cohort studies.



S3: Newcastle-Ottawa Quality Assessment Scale
Cohort Studies

Note: A study can be awarded a maximum of one star from each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. Evaluation of the study is circled in each category. (e.g. ⓐ ⓑ ⓒ ⓓ)

1. Reference ID: Antinori S, Cossu MV, Ridolfo AL, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post treatment hospitalization status. *Pharmacol Res* 2020. DOI: 10.1016/j.phrs.2020.104899

Selection

1) Representativeness of the exposed cohort
a. Truly representative of the average COVID-19 patients in the community.*
ⓑ Somewhat representative of the average COVID-19 patients in the community.*
c. Selected group of users e.g., nurses, volunteers
d. No description of the derivation of the cohort

2) Selection of the non-exposed cohort
ⓐ Drawn from the same community as the exposed cohort.
b. Drawn from a different source.
c. No description of the derivation of the non-exposed cohort.

3) Ascertainment of exposure
a. Secure record (e.g., surgical records) *
b. Structured interview *
c. Written self-report
d. No description

4) Demonstration that outcome of interest was not present at start of study
a. Yes *
b. No

Comparability

1) Comparability of cohorts on the basis of the design or analysis
a. Study controls for using non-intensive care hospitalization in infectious disease ward.
(select the most important factor)

Outcome

1) Assessment of outcome
a. Independent blind assessment
b. Record linkage *
c. Self-report
d. No description

2) Was follow-up long enough for outcomes to occur
a. Yes (select an adequate follow-up period for outcome of interest) *
b. No

3) Adequacy of follow up of cohorts
a. Complete follow up – all subjects accounted for *
b. Subjects lost to follow up unlikely to introduce bias – small number lost -> _17_% (select an adequate %) follow up, or description provided of those lost)
c. Follow up rate < _____ % (select an adequate %) and no description of those lost.

Newcastle-Ottawa Quality Assessment Scale
Cohort Studies

Note: A study can be awarded a maximum of one star from each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

2. Reference ID: Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2007016

Selection

5) Representativeness of the exposed cohort
a. Truly representative of the average COVID-19 patients in the community. *
b. Somewhat representative of the average COVID-19 patients in the community. *
c. Selected group of users e.g., nurses, volunteers
d. No description of the derivation of the cohort

6) Selection of the non-exposed cohort
a. Drawn from the same community as the exposed cohort.
b. Drawn from a different source.
c. No description of the derivation of the non-exposed cohort.

7) Ascertainment of exposure
a. Secure record (e.g., surgical records) *
b. Structured interview *
c. Written self-report
d. No description

8) Demonstration that outcome of interest was not present at start of study
a. Yes *
b. No

Comparability

2) Comparability of cohorts on the basis of the design or analysis
a. Study controls for using non-invasive ventilation.
(select the most important factor)

Outcome

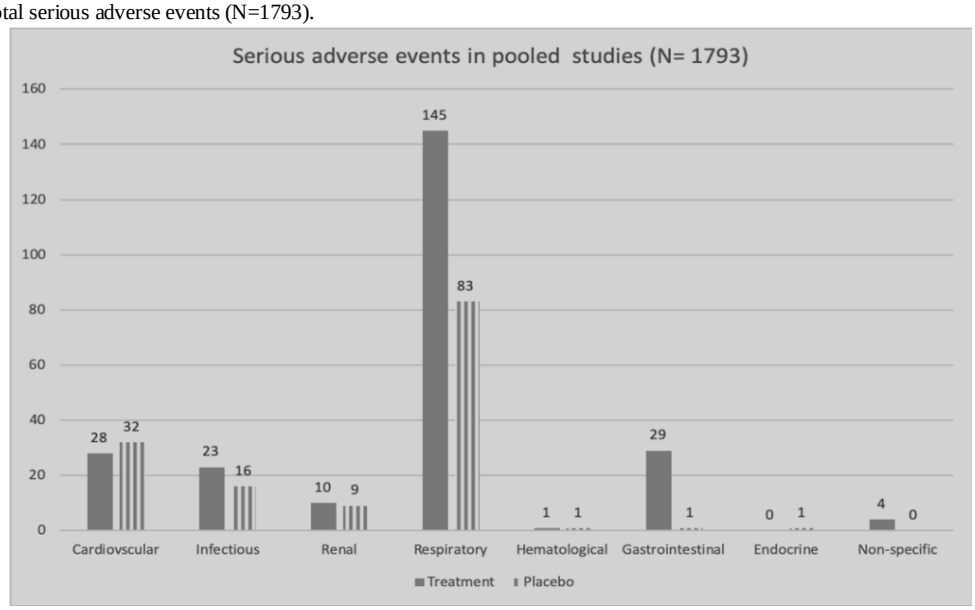
4) Assessment of outcome
a. Independent blind assessment
b. Record linkage *
c. Self-report
d. No description

5) Was follow-up long enough for outcomes to occur
a. Yes (select an adequate follow-up period for outcome of interest) *
b. No

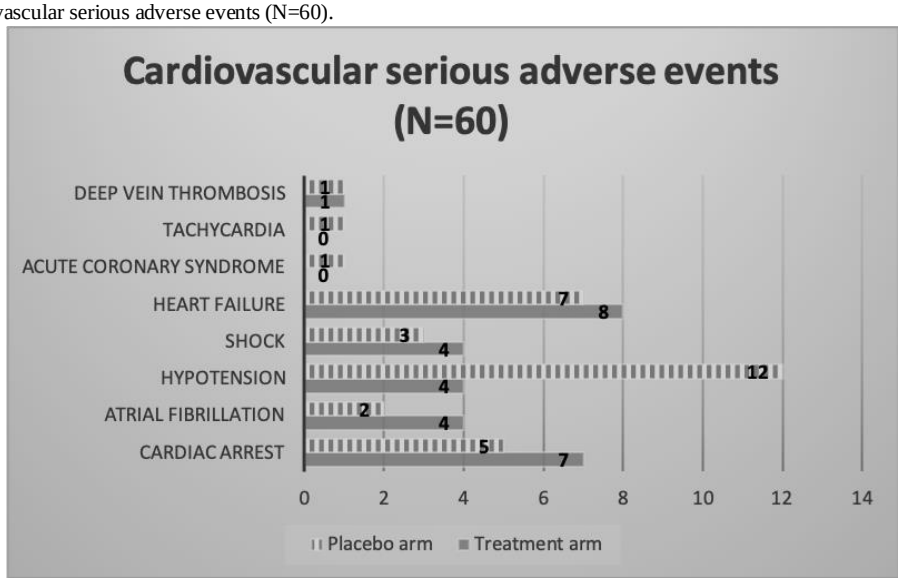
3) Adequacy of follow up of cohorts
a. Complete follow up – all subjects accounted for *
b. Subjects lost to follow up unlikely to introduce bias – small number lost -> _13_% (select an adequate %) follow up, or description provided of those lost)
c. Follow up rate < _____ % (select an adequate %) and no description of those lost.

S4: Serious Adverse Events Profile.

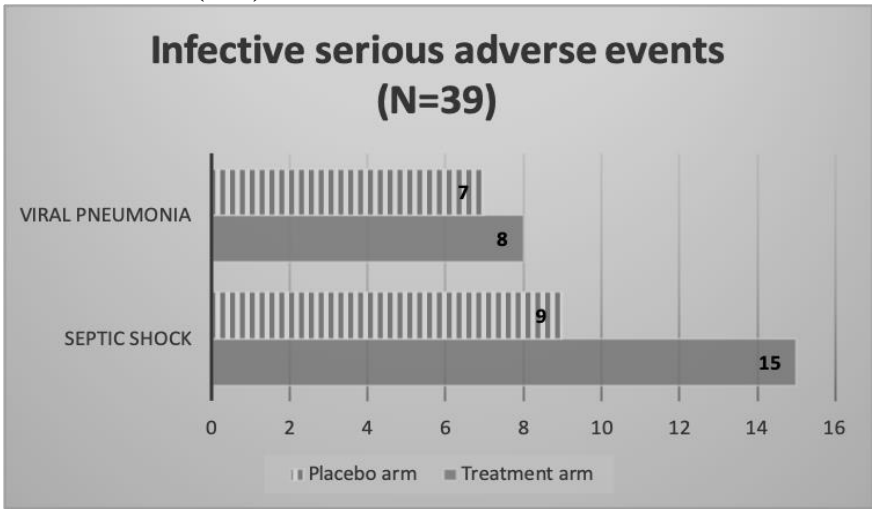
a) Total serious adverse events (N=1793).



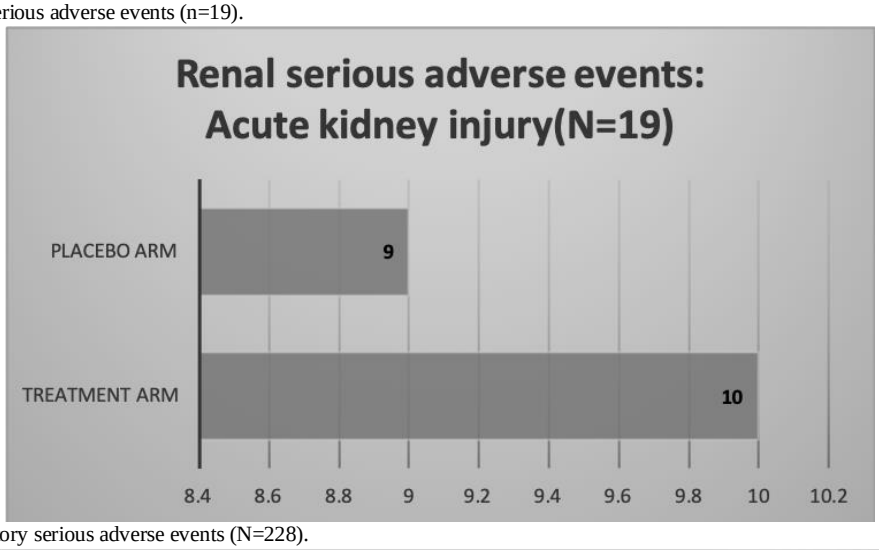
b) Cardiovascular serious adverse events (N=60).



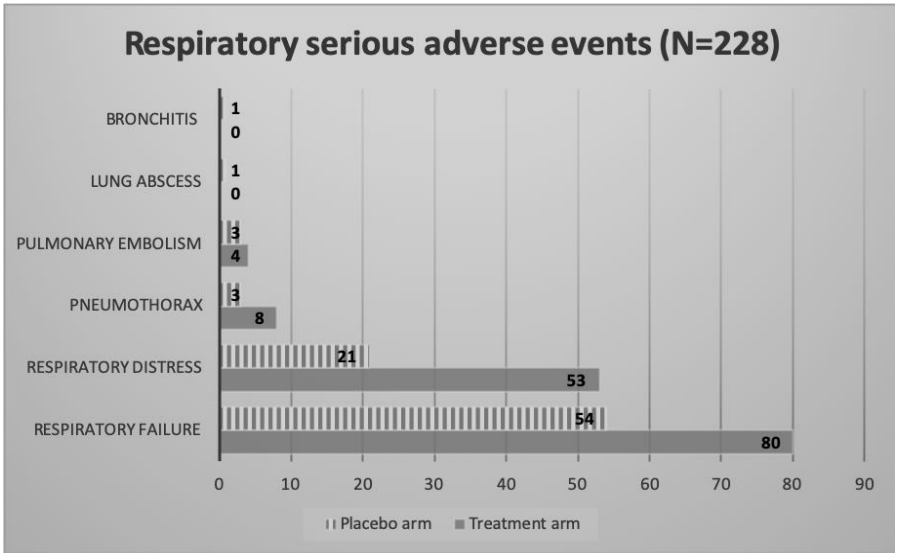
c) Infective serious adverse events (N=39).



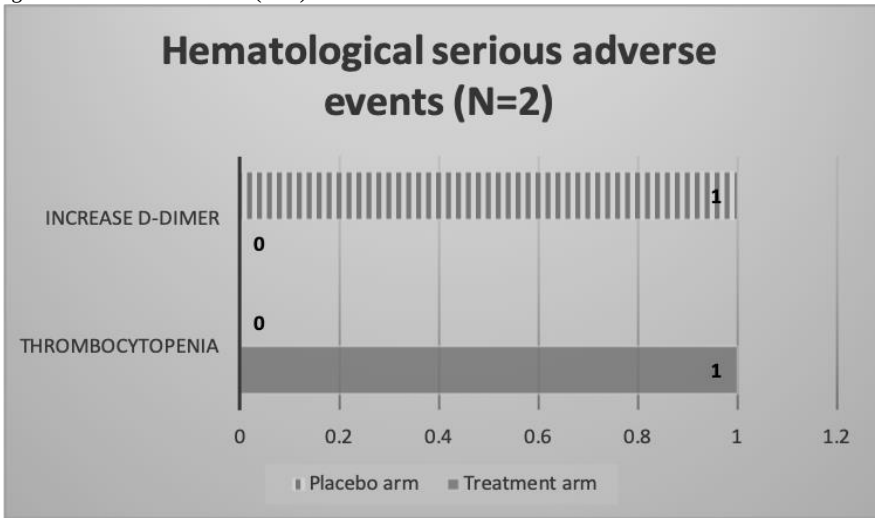
d) Renal serious adverse events (n=19).



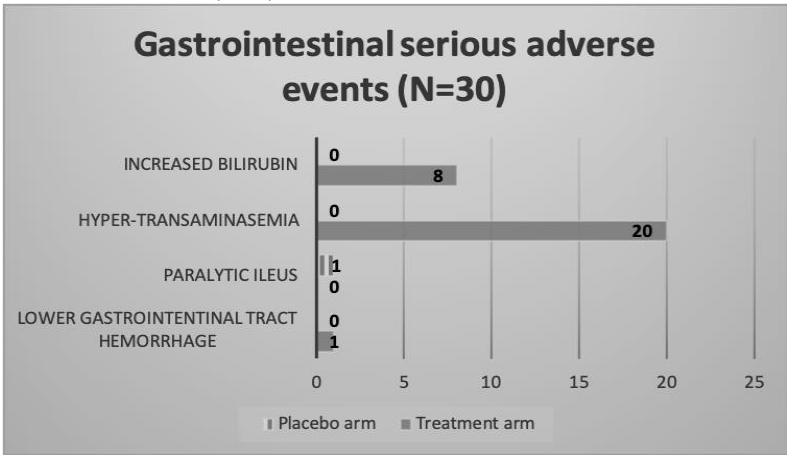
e) Respiratory serious adverse events (N=228).



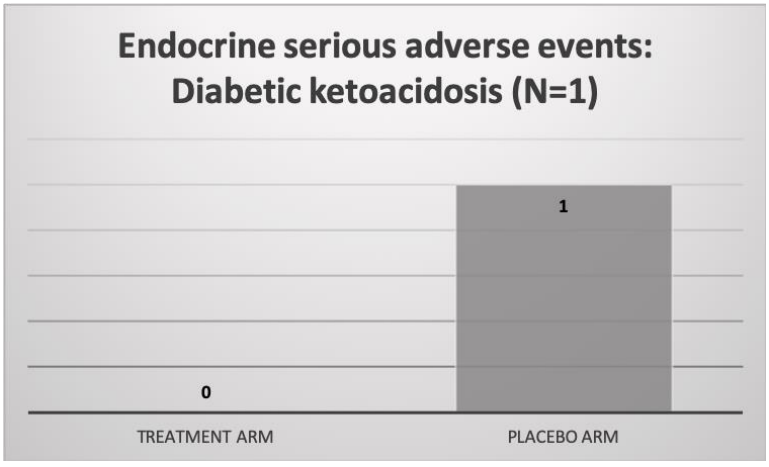
f) Hematological serious adverse events (N=2).



g) Gastrointestinal serious adverse events (N=30).



h) Endocrine serious adverse events (N=1).



i) Non-Specific serious adverse events (N=4).