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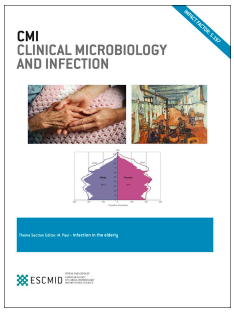

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PII: S1198-743X(22)00230-0

DOI: https://doi.org/10.1016/j.cmi.2022.04.018

Reference: CMI 2931

To appear in: *Clinical Microbiology and Infection*

Received Date: 16 March 2022

Revised Date: 19 April 2022

Accepted Date: 20 April 2022

Please cite this article as: Lee TC, Murthy S, Del Corpo O, Senécal J, Butler-Laporte G, Sohani ZN, Brophy JM, McDonald EG, Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2022.04.018.

Remdesivir for the Treatment of COVID-19: A Systematic Review and Meta-Analysis

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Word Count:
Abstract: 277
Text: 2257
Tables: 1
Figures: 3
References: 22

Key Words: Remdesivir, COVID-19, Coronavirus, Mortality, Meta-Analysis

Abstract

Background: The benefits of remdesivir in the treatment of hospitalized patients with Covid-19 remain debated with the National Institutes of Health and the World Health Organization providing contradictory recommendations for and against use.

Objectives: To evaluate the role of remdesivir for hospitalized inpatients as a function of oxygen requirements.

Data sources: Beginning with our prior systematic review, we searched MEDLINE using PubMed from January 15, 2021, through January 22, 2022.

Study eligibility criteria: Randomized controlled trials; all languages.

Participants: All hospitalized adults with Covid-19.

Interventions: Remdesivir, in comparison to either placebo, or standard of care.

Assessment of risk of bias: We used the ROB-2 criteria.

Methods of data synthesis: The primary outcome was mortality, stratified by oxygen use (none, supplemental oxygen without mechanical ventilation, and mechanical ventilation). We conducted a frequentist random effects meta-analysis on the risk ratio (RR) scale and, to contextualize the probabilistic benefits, we also performed a Bayesian random effects meta-analysis on the risk difference scale. A ≥1% absolute risk reduction was considered clinically important.

Results: We identified 8 randomized trials, totaling 9157 participants. The RR for mortality comparing remdesivir versus control was 0.71 (95% confidence interval [CI] 0.42-1.22) in the patients who did not require supplemental oxygen; 0.83 (95%CI 0.73-0.95) for nonventilated patients requiring oxygen; and 1.19 (95%CI 0.98-1.44) in the setting of mechanical ventilation. Using neutral priors, the probabilities that remdesivir reduces mortality were 74.7%, 96.9% and 8.9%, respectively. The probability that remdesivir reduced mortality by ≥1% was 88.1% for nonventilated patients requiring oxygen.

Conclusions: Based on this meta-analysis, there is a high probability that remdesivir reduces mortality for nonventilated patients with COVID-19 requiring supplemental oxygen therapy. Treatment guidelines should be re-evaluated.

Introduction

The World Health Organization (WHO) recommends against the use of remdesivir[1] for all patients with Covid-19, based primarily on the results of the SOLIDARITY trial, which failed to demonstrate a reduction in hospital length of stay or mortality [2]. Likewise, the American College of Physicians has recently concluded that "remdesivir probably results in little to no difference in mortality.[3]" By contrast, guidelines from the National Institutes of Health [4] and the Infectious Diseases Society of America [5] recommend the use of remdesivir in the treatment of Covid-19 for patients who do not require mechanical ventilation. These recommendations follow the completion of the Adaptive Covid-19 Treatment Trial 1 (ACTT-1) [6], which demonstrated a substantial decrease in hospital length of stay. On an international level, the benefits of remdesivir for the treatment of Covid-19 therefore remain debated and, in many countries, treatment with remdesivir may be underutilized. Indeed, only 20% of moderate-severe Covid-19 patients received remdesivir in a recent randomized controlled trial of baricitinib from the RECOVERY group [7].

We previously hypothesized that conflicting trial results relate to the differential effects of remdesivir as a function of the severity of the underlying illness. We tested this hypothesis in January 2021, when we conducted a Bayesian meta-analysis to determine the probability that remdesivir reduces mortality as a function of oxygen requirements [8]. Our findings suggested that the probability of any mortality benefit was 69% among patients without oxygen requirements, 92% in those requiring supplemental oxygen who were not ventilated, and only 7% among patients requiring mechanical ventilation. Though not assessed, the certainty of the evidence was low, rated down for imprecision and inconsistency or trial results. Since this time, two large new trials comparing remdesivir versus standard of care have been published [9,10]. We therefore conducted a systematic review and meta-analysis to clarify whether remdesivir reduces mortality in hospitalized patients with Covid-19.

Methods

Search Strategy, Study selection, and Data Extraction

We searched PubMed from January 1st, 2020, to January 21, 2022, to identify randomized controlled trials comparing remdesivir to placebo or standard of care in all hospitalized adults. There were no language restrictions. Newly identified trials were added to our previous results [8]. We used the search syntax "remdesivir AND (randomized OR randomised) AND 2021-01-

15[dp]:2022-01-21[dp]". Two independent reviewers screened for eligibility. Studies were included if they recruited hospitalized adult patients and reported either all-cause mortality or provided sufficient data to calculate all-cause mortality. There were no exclusion criteria. During peer review, the search was repeated using the Cochrane Library, which yielded no additional trials.

The primary outcome of interest was mortality, stratified by baseline oxygen support. Two reviewers independently extracted this data. Oxygen support was defined according to categories in the largest trial, SOLIDARITY, as: (i) no oxygen required; (ii) supplemental oxygen (without mechanical ventilation); and (iii) mechanical ventilation.

Assessment of Bias

Two independent reviewers assessed each study for bias using the Cochrane risk-of-bias 2 tool for randomized trials (version 2).

Meta-Analysis

The results are reported according to the PRISMA 2020 checklist[11]. All analysis was stratified by the level of oxygen support. We started with a frequentist analysis, as this is the method understood by most readers and because it provides for a more direct comparison with other systematic reviews of treatments for Covid-19. A Restricted Maximum Likelihood Estimation (REML) random effects meta-analysis on the risk ratio (RR) scale was used to undertake our frequentist analysis using the metan [12] command in STATA version 17 (STATACorp, USA). During peer review, two sensitivity analyses were conducted. First, we repeated the analysis excluding any trials where we were unable to exactly categorize all patients into the WHO SOLIDARITY oxygen support strata. Second, we repeated the analysis excluding trials at high risk of bias.

Next, to quantify the mortality benefit in absolute terms and to address clinically meaningful differences (*a priori* defined as the probability of achieving at least a 1% absolute mortality reduction), we conducted a Bayesian meta-analysis on the risk difference scale using R[13] and the bayesmeta package[14]. Vague proper non-informative priors were used: μ centered at 0 (standard deviation = 4), which corresponds to no effect; and heterogeneity τ assumed to be half-normal prior with a scale of 0.03 [8]. Figures of posterior density vs. absolute differences in mortality between remdesivir and control patients were generated, and we integrated the area

under the curve to obtain the probability for any mortality benefit and for a benefit exceeding 1% respectively [8].

Certainty Assessment

Certainty of evidence for mortality was assessed using the grading of recommendations assessment, development, and evaluation (GRADE) approach[15]. Two reviewers with familiarity and experience with GRADE rated each domain separately; discrepancies were resolved by consensus. Certainty was rated as high, moderate, low, or very low, based on the GRADE domains.

Results

The initial meta-analysis in January 2021 included 4 trials[8]; the present search yielded an additional 148 articles, of which 5 new trials were reviewed for eligibility for inclusion[9,10,16–18] (**Figure 1)**. One of the trials only contained patients previously reported in SOLIDARITY and was thus excluded[16]. A total of 8 RCTs were included in the present analysis (**Table 1**).

The trial by Spinner et al. [19] included children ages 12-17 but we were unable to uniquely identify their results. Children are at very low risk of mortality. Nonetheless, as the median age of all groups was 56-58 with IQRs ranged from 45-66, we believe that the data is representative of an adult population.

The DISCOVERY [10] and CATCO [9] trials were previously partially reported as part of the SOLIDARITY trial; therefore, to avoid duplication, we obtained data directly from the study teams on the subset of patients who were not already included in the SOLIDARITY report.

Results of the Mahajan et al.[18] study were not presented as intention-to-treat. We therefore reanalyzed their data using the intention-to-treat principle. We also included participants who were discharged before day 12 (categorized as alive), as well as those who died before day 12 (categorized as deceased).

Some trials deviated from the oxygen support categories described in the SOLIDARITY trial. We made the following adjustments to include them in our analyses. For the trial by Wang et al.[20], although study inclusion criteria required the use of oxygen, 3 patients in the placebo group were not receiving oxygen at the time of their first dose of remdesivir and there was one mechanically ventilated patient in the placebo group. We included all patients in the

'supplemental oxygen without mechanical ventilation' group. For the trial by Spinner et al.[19], although oxygen requirement was a study exclusion criterion, 14% and 19% of remdesivir and control patients, respectively, developed a need for supplemental oxygen between screening and the first dose of remdesivir. However, results were not reported by day 1 oxygen requirements. As most patients did not require supplemental oxygen, and due to the overall low mortality rate in both arms, we included this study in the 'no oxygen support' group. Next, the participants in the DISCOVERY trial[10] were classified according to disease severity. Moderate disease severity (no oxygen [16 total patients] and oxygen by nasal prongs or mask) and severe disease (high flow nasal oxygen, non-invasive, and invasive ventilation). We assigned the moderate group (n=223) to 'supplemental oxygen without mechanical ventilation' and the severe group (n=169) to 'mechanical ventilation'. Finally, the trial by Abd-Elsalam et al.[17] included mild and moderate severity patients with an average oxygen saturation of 87% and 89% in the remdesivir and control groups respectively. Although this study did not report results stratified by baseline oxygen requirements, mechanical ventilation was a trial exclusion criterion. We assigned these patients to the 'supplemental oxygen without mechanical ventilation' subgroup.

Included studies:

The meta-analysis includes 8 trials (**Table 1**) [2,6,9,10,17–20] comprising 9157 unique patients (2148 without oxygen, 5974 receiving supplemental oxygen without ventilation, and 1035 receiving mechanical ventilation; **Figure 2**). All but 2 studies[17,18] were considered at overall low risk for bias (**Supplemental Figure 1)**. While 6 of 8 studies were not placebo controlled, we believed there was low risk of bias considering the outcome of all-cause mortality.

Meta-analysis

With respect to the primary outcome of mortality, treatment with remdesivir was associated with a RR and 95% confidence interval (CI) of 0.71 (95%CI 0.42-1.22; I^2=0.0%) for patients without oxygen; 0.83 (95%CI 0.73-0.95; I^2=0.0%) for patients requiring oxygen, and 1.19 (95%CI 0.98-1.44; I^2=0.0%) for those on mechanical ventilation (**Figure 2)**. The results of the two sensitivity analyses were largely consistent (**Supplemental Figures 2 and 3**). On the risk difference scale, for patients without oxygen the probability of any mortality benefit was 74.7%, for those requiring oxygen 96.9%, and for those on mechanical ventilation was 8.9% (**Figure 3**). For patients requiring oxygen without the need for mechanical ventilation, the mean estimate for the absolute

risk difference was 2.4% and the probability that the absolute risk reduction was ≥1% was 88.1%.

GRADE Certainty of Evidence

Regarding the overall certainty of the evidence, the primary outcome of our analysis was mortality, which is not likely subject to adjudication bias. However, most of the included studies were open label, and some evidence suggest that the effect size for mortality might be slightly lower with placebo control [21]. There was also the potential for some misclassification of oxygen requirements, reducing the overall certainty of the evidence away from high. The probability of benefit in the oxygenated subgroup, and correspondingly of harm in the mechanical ventilation subgroup (91.1%), were both high. In these respective subgroups, a recommendation for and against remdesivir is proposed with moderate certainty. It should be noted that participants requiring high flow nasal cannula and non-invasive ventilation were underrepresented in the included trials rendering the certainty of evidence low for this subgroup. Finally, the suggestion of a mortality benefit in patients who do not require oxygen is also of low certainty, given the probability of a meaningful effect was very modest. The results were also downgraded for inconsistency as there remained a 25.3% probability of increased mortality, and there were very few patients who died in either group.

Discussion

Our meta-analysis comparing remdesivir versus placebo or standard of care suggests a high probability of a clinically meaningful reduction in mortality for patients requiring supplemental oxygen. Although an analysis of remdesivir trials stratified by oxygen requirements is *post hoc*, the ACTT-1 trial[6] already suggested a potential mortality benefit for patients in the “Goldilocks zone” (disease severity requiring oxygen without needing critical care). By contrast, we found a high probability that remdesivir harms patients requiring mechanical ventilation and that any beneficial effect size is much smaller for patients who did not require any supplemental oxygen.

There are still unanswered questions related to remdesivir treatment in hospitalized patient subgroups, which could be the focus of future randomized trials. For example, whether there is a benefit in early nosocomial Covid-19, or “incidental” non-hypoxemic Covid-19 for patients at high risk for deterioration. This could be akin to the benefit observed in the recent PINETREE trial that demonstrated superiority of 3 days of remdesivir versus placebo in high risk outpatients [22]. Likewise, the role of remdesivir in the setting of high flow nasal oxygen or non-invasive

ventilation needs to be clarified as, to date, this population is less represented in trials, or the total data is not sufficiently granular.

The strengths of this analysis are the avoidance of duplicated patients despite the inclusion of published SOLIDARITY country-level studies, our *a priori* decision to stratify the analysis by oxygen requirements, and the consistent and complimentary results of the frequentist and Bayesian analysis. The later allows us to contextualize the probability of a clinically meaningful reduction in mortality from remdesivir in a way that the relative risk does not.

There are limitations to this analysis, the principal one being that the standard of care for Covid-19 continues to evolve at a staggering pace. Earlier in the pandemic, trial participants were less likely to receive treatments now known to reduce adverse outcomes including steroids, monoclonal antibodies, immunomodulatory therapies, or therapeutic anticoagulation. Additionally, very few of the participants included in this analysis were vaccinated against Covid-19 and all results predate the delta and omicron variants. It is unlikely that there will be additional large randomized controlled trials of remdesivir in vaccinated patients or with newer variants remains and this makes inferences about the magnitude of benefit of remdesivir in these populations challenging. While we feel confident (moderately certain) about the inferences made for patients who require oxygen or mechanical ventilation, it is important to note that there were very few deaths in patients who did not require oxygen. A mortality benefit in this group presumably needs to be better delineated in the context of modern therapy and the baseline risk of the patient. A final limitation we wish to note is a small lack of granularity with respect to oxygen requirements for a handful of patients; however, in our sensitivity analyses which excluded those trials, there were only very small differences in the estimate of relative risk reduction. An individual patient meta-analysis could provide more precise results and transparent data reporting and while data sharing is welcomed, we recognize the complexities of conducting such a multinational study.

Conclusions

There is a high probability (97%) that remdesivir reduces mortality for patients who require oxygen but who are not yet critically ill. Future antiviral treatment trials for noncritically ill hospitalized patients with Covid-19 should likely include remdesivir as an active treatment arm, stratified by oxygen requirements. Importantly, we hope the results of this meta-analysis support harmonization of discrepant international guideline recommendations and facilitate the appropriate uptake of remdesivir in certain patient populations.

CRediT Author Statement

The first author named is the lead author and corresponding author. The last author is the senior author. We describe contributions to the paper as follows:

Conceptualization – TCL and EGM; *Methodology* – TCL, and JMB; *Validation* – TCL; *Formal analysis* – TCL and JMB; *Data Curation* – TCL, SM, ODC, JS, and GBL; *Writing – Original Draft* – TCL *Writing – Review and Editing* – all listed; *Visualization* – TCL, JMB and EGM; *Supervision* – TCL.

Conflict of interest

Dr. Murthy was the principal investigator and Dr. Lee was a co-investigator on CATCO, the Canadian arm of the WHO SOLIDARITY trial which was funded by the Canadian Institutes of Health Research (CIHR). Dr. Murthy was awarded a competitive research chair in pandemic preparedness at the University of British Columbia that is funded by the Health Research Foundation of Innovative Medicines Canada. No other author has received financial support from the pharmaceutical industry within the last 3 years.

Funding

Drs Lee, McDonald, and Brophy receive research salary support from the Fonds de Recherche Québec - Santé. Dr Butler-Laporte is supported by a scholarship from the Fonds de Recherche Québec - Santé and the Ministère de la Santé et des Services sociaux. The CATCO trial was funded by the Canadian Institutes of Health Research (CIHR). The funders had no influence on the conduct or content of this article.

Ethical approval

Not required.

Registration

As this was an update of previous work based on newly published information, this systematic review was not pre-registered, and a specific protocol was not prepared.

Data Sharing

All data required to replicate this analysis is included in the manuscript. Statistical code is available for audit upon written request.

Acknowledgements

The authors wish to thank all the DISCOVERY trial team and the CATCO team for providing the unpublished data required to complete this analysis.

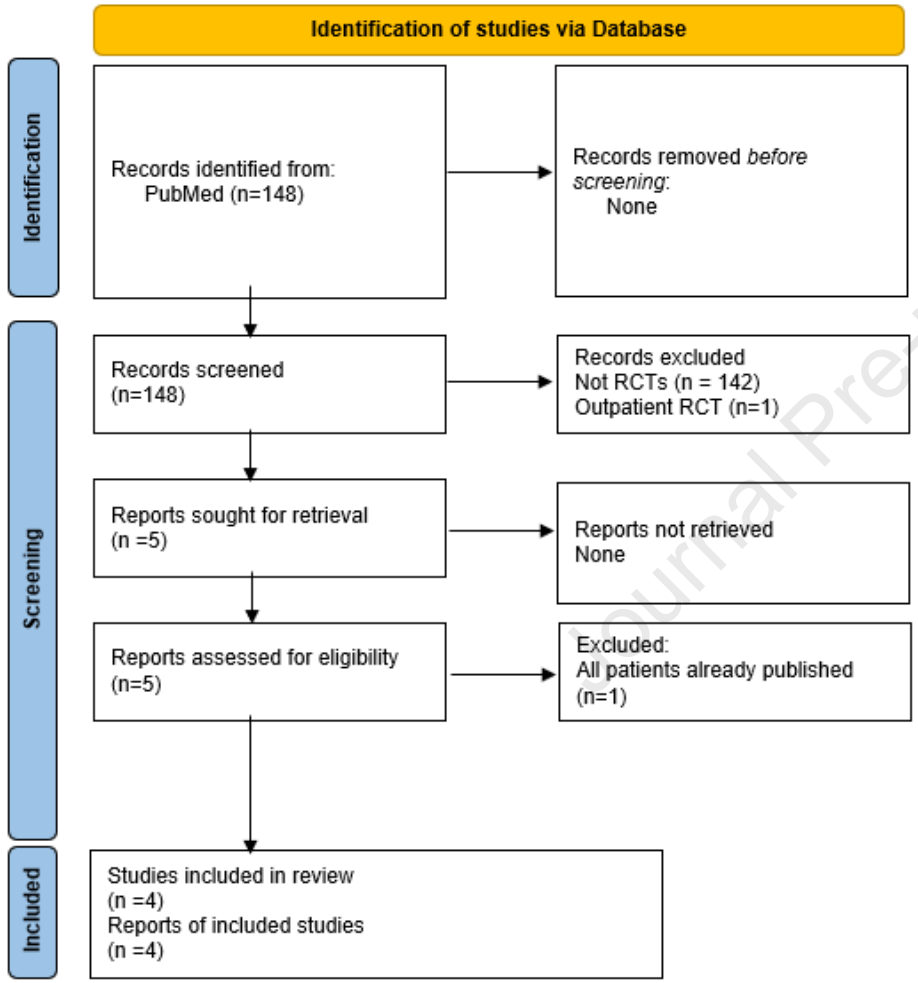
Table 1 – Description of Included Trials

Paper	Study Design	Population	Stratification	Number of patients in ITT	Primary Trial Outcome	Steroids
Abd-Elsalam 2021	Open label	Patients admitted to hospital 3-days after onset of symptoms with PCR confirmed COVID. Inclusion criteria involved patient with mild to moderate disease aged 18-80 according to Egyptian national guidelines (RR 20-30, fever above 38, myalgia/sore throat, chest infection). Exclusion: renal impairment, ALT or AST>5 times limit of normal, allergy to remdesivir, pregnant or lactating.	1:1 Patients received remdesivir (10d) with standard of care vs versus standard care alone.	Remdesivir: 100 Control: 100	Length of hospital stay from randomization to discharge, and mortality rate.	No data
Ader 2021 (DISCOVERY)	Open label	Patients 18 and over admitted with confirmed SARS-CoV-2 infections and illness of any duration if they presented with the following: oxygen saturation of 94 or less on room air, requirement of supplemental oxygen, NIV or mechanical ventilation. Exclusion: AST or ALT > 5 times limit or normal, dialysis, breastfeeding, or transfer within 72h.	Participants randomly assigned 1:1:1:1:1 when 5 groups were implemented and were then assigned to 1:1 to receive either standard of care or standard plus remdesivir (10d). Severe disease: patients with NIV, high flow oxygen devices, mechanical ventilation, ECMO.	Remdesivir: 406 Control: 418 195 and 197 not included in SOLIDARITY.	Clinical status at day 15 as measured by WHO master protocol.	40% of patients received systemic corticosteroids.
Beigel 2020 (ACTT-1)	Placebo controlled	Patients over 18 years admitted to the hospital with a PCR proven SARS-CoV-2 infection and evidence of lower respiratory tract infection (defined by oxygen saturation, requirement of oxygen supplementation or ventilation, or by radiologic tests). Exclusion: ALT/AST>5 times limit of normal, eGFR<30 or dialysis, pregnant or breast feeding, allergy to medication, or anticipated/transfer discharge ≤ 72 hours.	1:1 assignment to remdesivir (10d) or placebo, with local hospital standard of care.	Remdesivir: 541 Control: 521	Time to recovery (category 1-3 on the WHO scale).	23% of patients received systemic corticosteroids.
CATCO 2021	Open label	Patients 18 and over with laboratory confirmed SARS-CoV-2 infections. Exclusion: allergy to study drug, anticipated transfer to non-study site, expected survival ≤24h or already receiving remdesivir at time of enrolment.	Patients were randomized unstratified 1:1 to receive treatment regimen of remdesivir (10d) plus standard of care or standard of care alone.	Remdesivir: 634 Control: 647 579 and 582 not included in SOLIDARITY.	In hospital mortality.	87% of patients received systemic corticosteroids.
Mahajan 2021	Open label	Inclusion: hospitalized patients between 18-60 years with PCR proven SARS-CoV-2 infection within the previous 4 days, with evidence of COVID-19 based on radiology, respiratory rate > 24/min, or oxygen saturation < 94% on room air. Exclusion: mechanical ventilation, multiorgan failure, CrCl<40, or AST or ALT > 3 times limit of normal.	1:1 Patients stratified to 200mg remdesivir (5d) + standard of care vs. standard of care alone	Remdesivir: 41 Control: 41	Time to recovery.	No data

Pan 2020 (SOLIDARITY)	Open label	Patients 18 years and over hospitalized with a diagnosis of SARS-CoV-2, were not known to receive any trial drug, not expected to be transferred and had no contraindication to any trial drug.	The trial drugs were remdesivir (10d), hydroxychloroquine, lopinavir and interferon beta-1a. Participants were randomly assigned in equal proportions to receive standard of care or one of the trial drug regimens.	Remdesivir: 2743 Control: 2708	In hospital mortality regardless if death occurred before or after day 28.	48% of patients received systemic corticosteroids
Spinner 2020	Open label	Patients 12 and over with SARS-CoV-2 infections confirmed by PCR within 4 days of randomization. Patients 12 to 17 needed to weight at least 40kg for inclusion. Patients needed to have radiographic evidence of pulmonary infiltrate with an oxygen saturation > 94% on room air at screening. Exclusion: mechanical ventilation, ALT or AST > 5x limit of normal, CrCl < 50, pregnancy, breastfeeding, known hypersensitivity to the drug, the metabolites, or excipient.	Patients were randomly assigned in a 1:1:1 ratio to receive up to a 5-day course of remdesivir, up to a 10-day course of remdesivir, or standard care.	Remdesivir: 384 (193 10d; 191 5d) Control: 200	7-point ordinal scale on study day 11.	16% of patients received systemic corticosteroids.
Wang 2020	Placebo controlled	Eligible patients were men and non-pregnant women with COVID-19 who were aged at least 18 years and were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxy- gen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset. Exclusion: pregnancy or breast feeding; cirrhosis; ALT or AST >5 times limit of normal; eGFR<30; dialysis; possibility of transfer to a non-study hospital ≤72h.	Eligible patients were randomly assigned (2:1) to either the remdesivir (10d) group or the placebo group.	Remdesivir: 158 Control: 79 (1 withdrew consent)	Time to clinical improvement.	65% of patients received systemic corticosteroids.

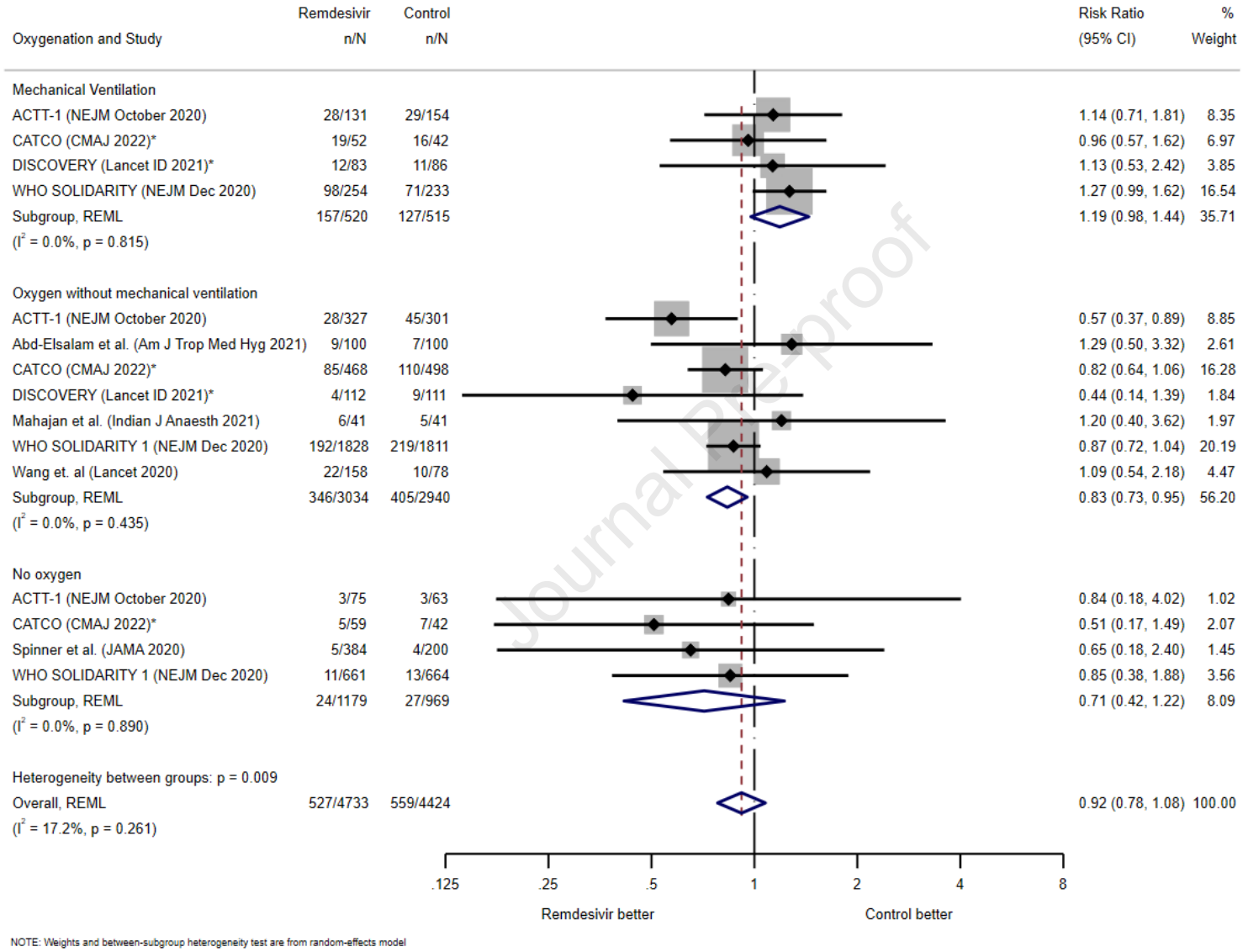
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; NIV: non-invasive ventilation; ECMO: extracorporeal membrane oxygenation; WHO: World Health Organization; eGFR: estimated glomerular filtration rate; CrCl: Creatinine clearance

Figure 1 – PRISMA diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

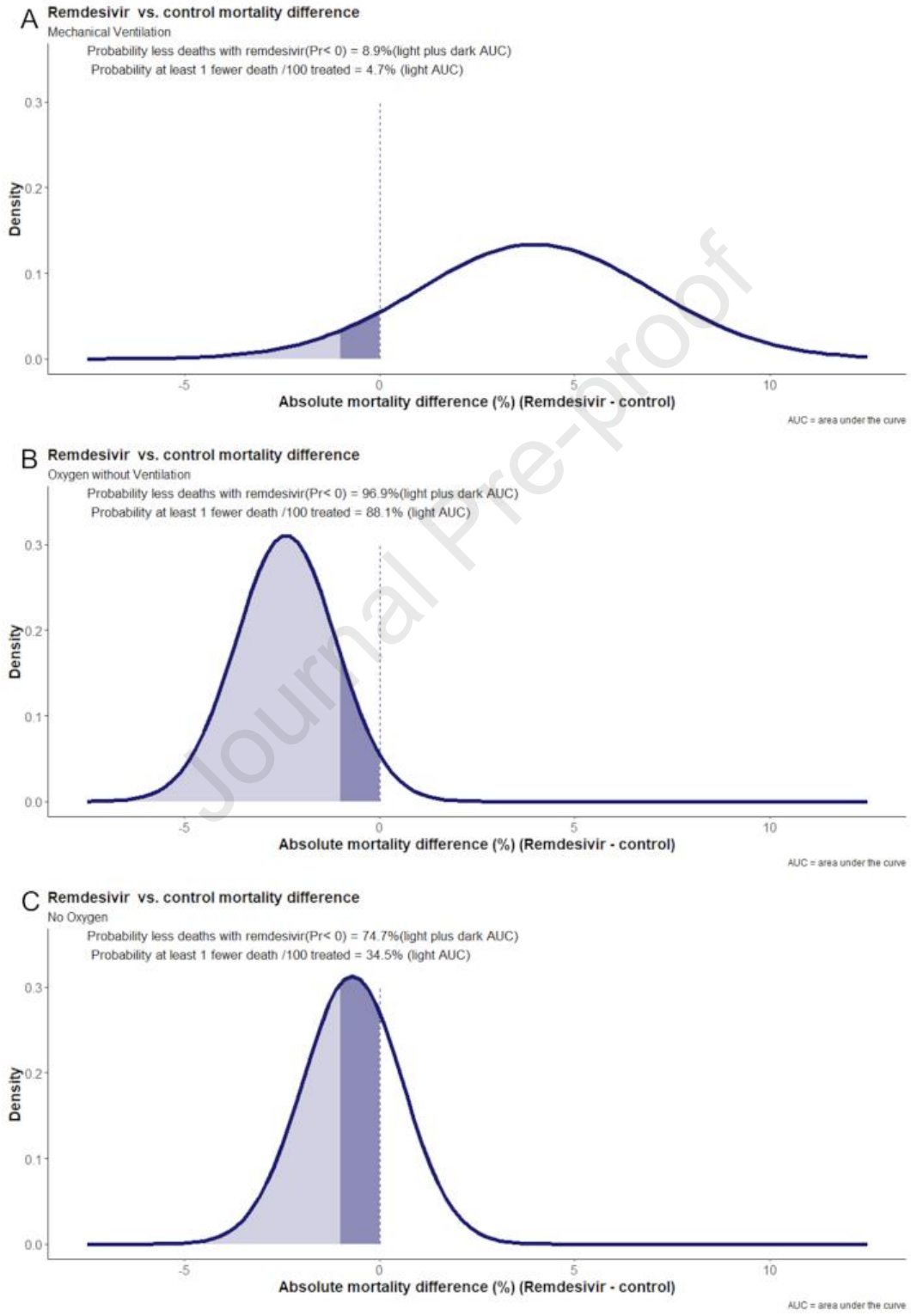
Figure 2 – Random Effects Meta-Analysis



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

*Excludes patients already included in SOLIDARITY (NEJM 2020)

Figure 3 – Probability density functions for combined posterior distributions of the included remdesivir trials. (A) Mechanical ventilation. (B) Supplemental oxygen without mechanical ventilation. (C) No oxygen support.



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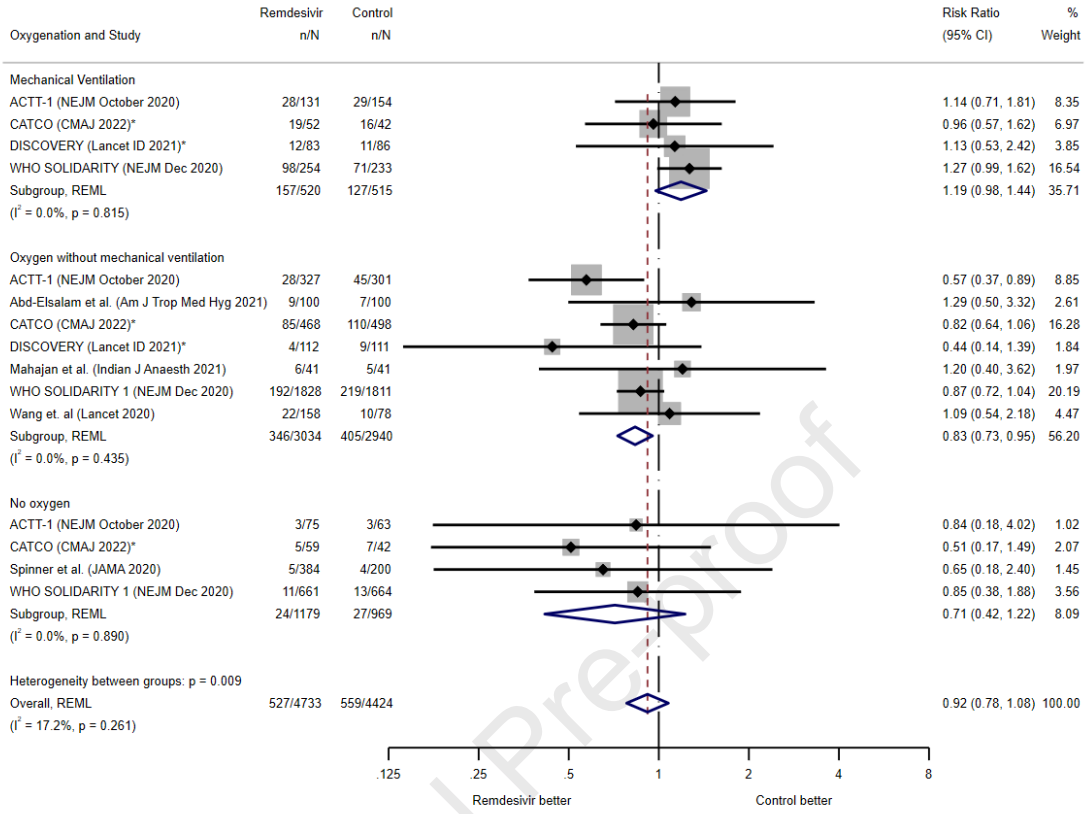

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model