Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Systematic review

Remdesivir for the treatment of COVID-19: a systematic review and meta-analysis

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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 15 January 2021 through 5 May 2022.
Study eligibility criteria: Randomised 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 scale and, to contextualize the probabilistic benefits, we also performed a Bayesian random effects meta-analysis on the risk difference scale. A $\geq$1% absolute risk reduction was considered clinically important.
Results: We identified eight randomized trials, totaling 10 751 participants. The risk ratio for mortality comparing remdesivir vs. control was 0.77 (95% CI, 0.5–1.19) in the patients who did not require supplemental oxygen; 0.89 (95% CI, 0.79–0.99) for nonventilated patients requiring oxygen; and 1.08 (95% CI, 0.88–1.31) in the setting of mechanical ventilation. Using neutral priors, the probabilities that remdesivir reduces mortality were 76.8%, 93.8%, and 14.7%, respectively. The probability that remdesivir reduced mortality by $\geq$ 1% was 77.4% 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. **Todd C. Lee, Clin Microbiol Infect 2022;28:1203**

Introduction

The 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

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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 (RCT) 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. Although 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 vs. 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 1 January 2020 to 21 January 2022, to identify RCTs 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 and updated to May 2022 to include the final publication from SOLIDARITY [11].

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 (a) no oxygen required, (b)

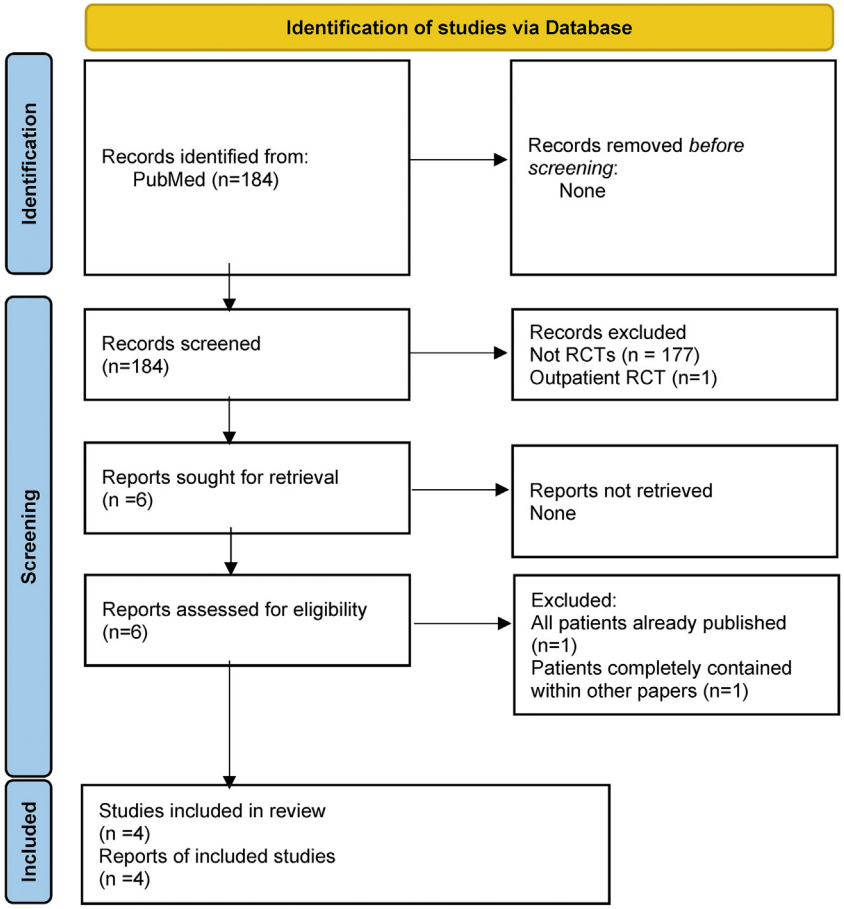

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Fig. 1. PRISMA diagram for the systematic review and meta-analysis. RCT: Randomized controlled trial.

Table 1
Description of included trials

Paper	Study design	Population	Stratification	Number of patients in ITT	Primary trial outcome	Steroids
Abd-Elsalam et al. [18]	Open label	Patients admitted to hospital 3 d after onset of symptoms with PCR confirmed COVID-19. Inclusion criteria involved patient with mild to moderate disease aged 18−80 y 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 (10 d) with standard of care vs. standard of care alone.	Remdesivir: 100 Control: 100	Length of hospital stay from randomization to discharge, and mortality rate.	No data
Beigel, 2020 (ACTT-1)	Placebo controlled	Patients aged >18 y 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 breastfeeding, allergy to medication, or anticipated/transfer discharge ≤72 hours.	1:1 assignment to remdesivir (10 d) 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 y with laboratory confirmed SARS-CoV-2 infections. Exclusion: allergy to study drug, anticipated transfer to non-study site, expected survival ≤24 hours or already receiving remdesivir at time of enrolment.	Patients were randomized unstratified 1:1 to receive treatment regimen of remdesivir (10 d) 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 aged between 18−60 y with PCR proven SARS-CoV-2 infection within the previous 4 d, with evidence of COVID-19 based on radiology, respiratory rate >24 breaths/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 200 mg remdesivir (5 d) + standard of care vs. standard of care alone.	Remdesivir: 41 Control: 41	Time to recovery.	No data
Pan, 2020 (SOLIDARITY)	Open label	Patients aged ≥18 y 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 (10 d), 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
Pan, 2022 (SOLIDARITY)	Open label	Patients aged ≥18 y 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 (10 d), 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: 4146 (1403 new) Control: 4129 (1421 new)	In-hospital mortality regardless if death occurred before or after day 28.	68% of patients received systemic corticosteroids
Spinner, 2020	Open label	Patients aged ≥12 y with SARS-CoV-2 infections confirmed by PCR within 4 d of randomization. Patients aged 12−17 y needed to weight at least 40 kg 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 >5 times limit of normal, CrCl <50, pregnancy,	Patients were randomly assigned in a 1:1:1 ratio to receive up to a 5-d course of remdesivir, up to a 10-d course of remdesivir, or standard of care.	Remdesivir: 384 (193 10 d; 191 5 d) Control: 200	7-point ordinal scale on study day 11.	16% of patients received systemic corticosteroids.

(*continued on next page*)

Table 1 (*continued*)

Paper	Study design	Population	Stratification	Number of patients in ITT	Primary trial outcome	Steroids
		breastfeeding, known hypersensitivity to the drug, the metabolites, or excipient.				
Wang, 2020	Placebo controlled	Eligible patients were men and non-pregnant women with COVID-19 who were aged ≥18 y 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 oxygen partial pressure to fractional inspired oxygen of 300 mmHg or less, and were within 12 d of symptom onset. Exclusion: pregnancy or breastfeeding, cirrhosis, ALT or AST >5 times limit of normal, eGFR <30, dialysis, possibility of transfer to a non-study hospital ≤72 hours.	Eligible patients were randomly assigned (2:1) to either the remdesivir (10 d) 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; CrCl, creatinine clearance; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; NIV, non-invasive ventilation; RR, risk ratio.

supplemental oxygen (without mechanical ventilation), and (c) mechanical ventilation.

Assessment of bias

Two independent reviewers assessed each study for bias using the Cochrane risk-of-bias 2 tool for randomized trials (v2).

Meta-analysis

The results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist [12]. 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 random effects meta-analysis on the risk ratio (RR) scale was used to undertake our frequentist analysis using the metan [13] command in STATA v17 (STATACorp, College Station, TX, 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 considered 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 [14] and the bayesmeta package [15]. The following 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 [16]. 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 four trials [8]; the updated search yielded an additional 184 articles, of which 6 new trials were reviewed for eligibility for inclusion [9–11,17–19] (Fig. 1). Two of the trials only contained patients completely reported in SOLIDARITY and were thus excluded [10,17]. A total of eight RCTs were included in the present analysis (Table 1).

SOLIDARITY was published as two manuscripts—an interim report in late 2020 in the *New England Journal of Medicinie* [2], and a final report in May 2022 in the *Lancet* [11]. Of note, neither a prespecified sample size nor stopping rules were published in either report. When comparing the two reports, it was evident that mortality in all groups was almost two-fold higher in patients recruited after the interim report compared to those recruited prior. We thus decided *a priori* to analyse the two SOLIDARITY reports separately. We took this approach to account for the unique pandemic situation whereby between the first and second report

there were clear differences in patient outcomes, major changes occurred with respect to disease co-management (e.g., adjunctive steroids), and to account for the absence of a predefined sample size or stopping rules.

The initial patients in the CATCO [9] trial were previously partially reported as part of the SOLIDARITY trial [2]; therefore, to avoid duplication, we obtained data directly from the CATCO team on the subset of patients who were included in the first and second SOLIDARITY reports. Similar to the above, we included CATCO independently of SOLIDARITY 2022 [11]. We justified this because CATCO continued to randomize an additional 323 patients even after SOLIDARITY had stopped and they also published their results independently in January 2022 [9].

The trial by Spinner et al. [20] included children aged 12–17 years, 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 years with interquartile ranges ranged from 45–66, we believe that the data are overall representative of an adult population.

Results of the Mahajan et al. [19] study were not presented as intention to treat. We therefore reanalysed 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. [21], although study inclusion criteria required the use of oxygen, three 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. [20], 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. Finally, the trial by Abd-Elsalam et al. [18] 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 eight trials (Table 1) [2,6,9,11,18–21] comprising 10 751 unique patients (2473 without oxygen, 7266 receiving supplemental oxygen without ventilation, and 1012 receiving mechanical ventilation; Fig. 2). All but two studies [18,19] were considered at overall low risk for bias (see Supplementary material, Fig. S1). While 6 of 8 studies were not placebo controlled, we believed there was low risk of bias considering the outcome of all-cause mortality.

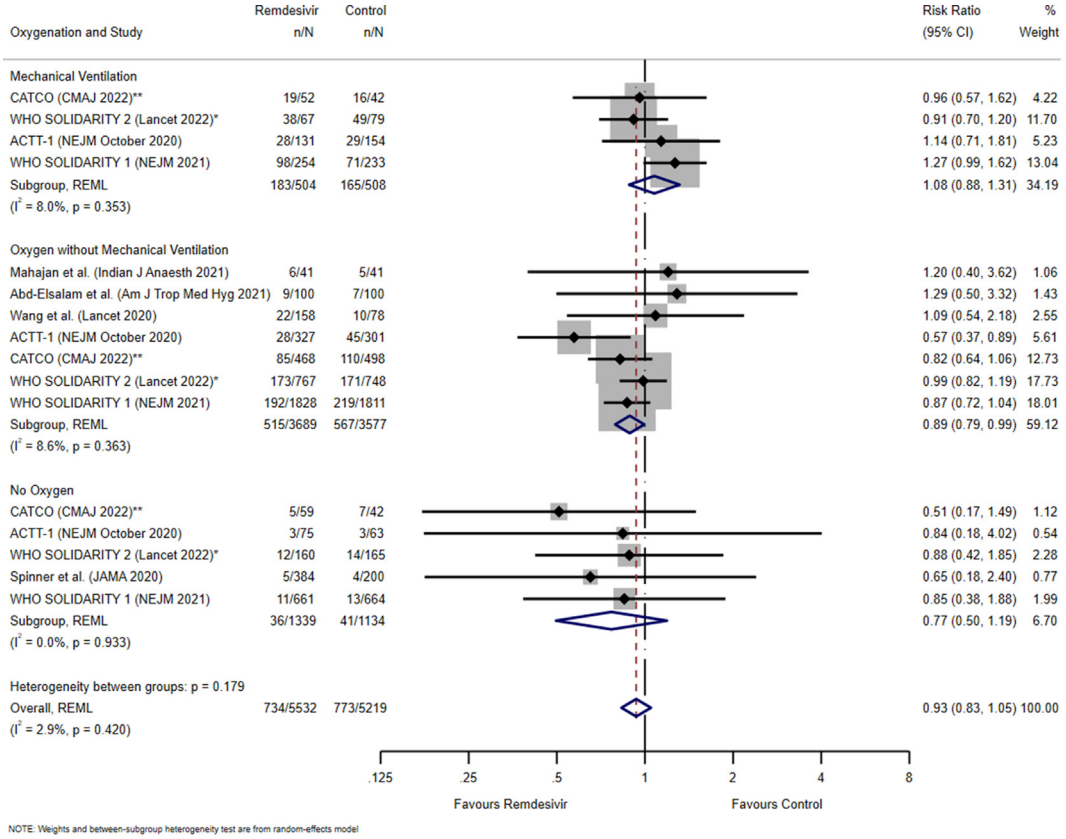

Fig. 2. Random effects meta-analysis stratified by oxygenation requirements. *Excludes patients already reported in SOLIDARITY 1 (NEJM 2020) and CATCO (CMAJ 2022); **Excludes patients reported in SOLIDARITY 1 (NEJM 2022). ACTT: Adaptive Covid-19 Treatment Trial. CATCO: Canadian Treatments for COVID-19.

Meta-analysis

With respect to the primary outcome of mortality, treatment with remdesivir was associated with a RR and 95% CI of 0.77 (95% CI, 0.50–1.19; $I^2 = 0.0\%$) for patients without oxygen; 0.89 (95% CI, 0.79–0.99; $I^2 = 8.6\%$) for patients requiring oxygen, and 1.08 (95% CI, 0.88–1.31; $I^2 = 8.0\%$) for those on mechanical ventilation (Fig. 2). The results of the two sensitivity analyses were largely consistent (see Supplementary material, Figs S2 and S3). On the risk difference scale, for patients without oxygen the probability of any mortality

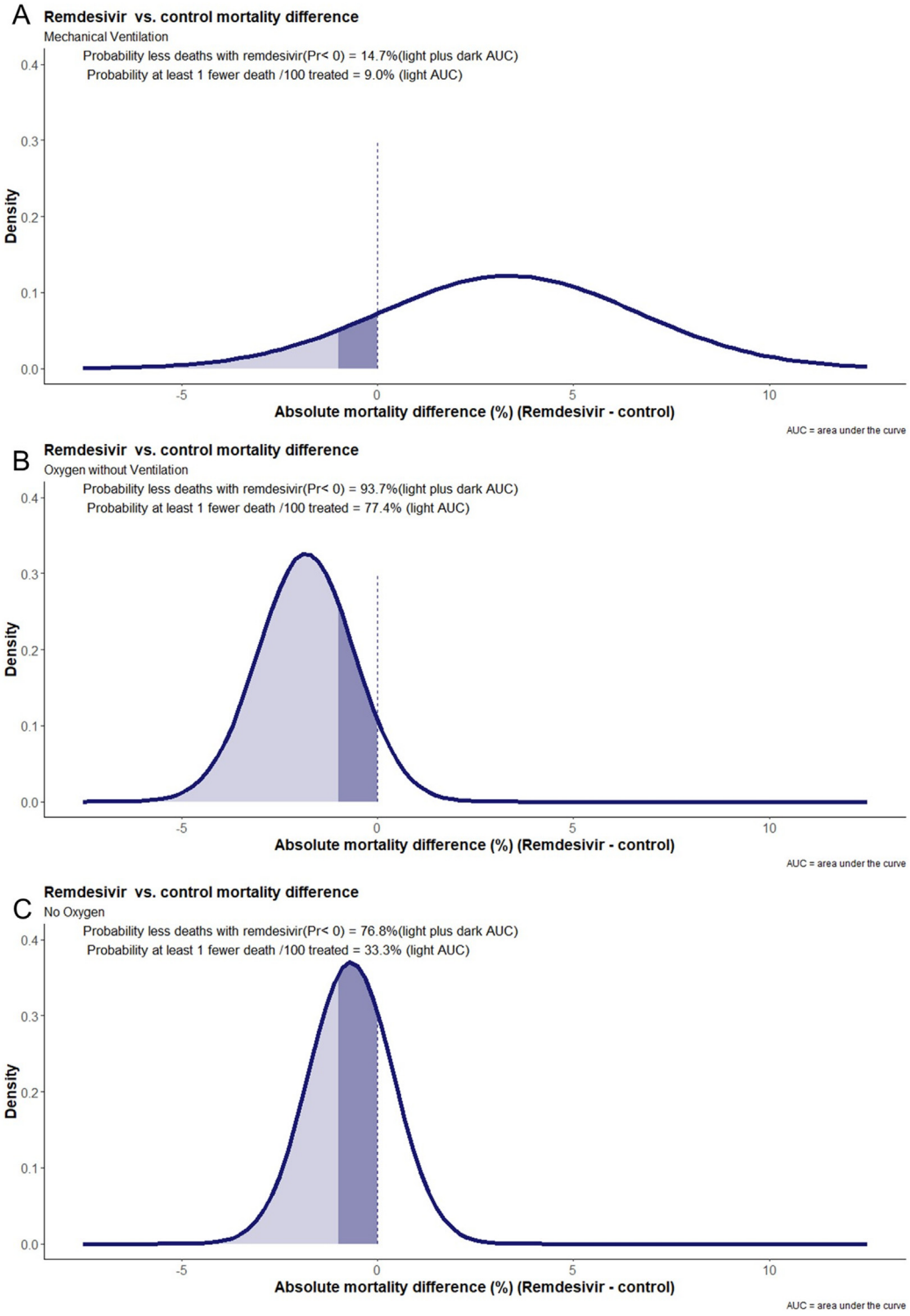

Fig. 3. Probability density functions for combined posterior distributions of the included remdesivir trials. (a) Mechanical ventilation. (b) Supplemental oxygen without mechanical ventilation. (c) No oxygen support. AUC, area under the curve.

benefit was 76.8%, for those requiring oxygen 93.8%, and for those on mechanical ventilation was 14.8% (Fig. 3). For patients requiring oxygen without the need for mechanical ventilation, the mean estimate for the absolute risk difference was 1.8% and the probability that the absolute risk reduction was $\geq$1% was 77.4%.

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 suggests that the effect size for mortality might be slightly lower with placebo control [22]. 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 corresponding probability of harm in the mechanical ventilation subgroup (85.2%) 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 23.2% probability of increased mortality, and there were very few patients who died in either group.

Discussion

Our meta-analysis comparing remdesivir vs. 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 supplemental oxygen.

There are still unanswered questions related to remdesivir treatment in hospitalized patient subgroups, which could be the focus of future randomised 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 vs. placebo in high-risk outpatients [23]. 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 are 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 RCTs of remdesivir in vaccinated patients or with newer variants 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 estimates of relative risk reduction. An individual patient meta-analysis could provide more precise results and while data sharing is welcomed, we recognize the complexities of conducting such a multinational study.

Conclusions

There is a high probability (94%) 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.

Transparency declaration

S.M. was the principal investigator and T.C.L. 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) grant numbers 422549, 446637 and 424701. S.M. 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.

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Author contributions

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 – T.C.L. and E.G.M.; methodology – T.C.L. and J.M.B.; validation – T.C.L.; formal analysis – T.C.L. and J.M.B.; data curation – T.C.L., S.M., O.D.C., J.S., and G.B.L.; writing – original draft – T.C.L.; writing – review and editing – all listed; visualization – T.C.L., J.M.B., and E.G.M.; supervision – T.C.L.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.04.018.

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