

Remdesivir for coronavirus disease 2019 (COVID-19): a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials

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ABSTRACT

Background: In view of many unanswered clinical questions regarding treatment of COVID-19 with remdesivir, we systematically identified, critically appraised and summarized the findings from randomized controlled trials (RCTs) of remdesivir for COVID-19.

Methods: We searched relevant databases/websites (up to September 2020) and selected English-language RCT publications of remdesivir for COVID-19. We conducted meta-analysis using an inverse variance, random-effects model in addition to trial sequential analysis (TSA) for the efficacy outcomes: all-cause mortality, viral burden and clinical progression. Safety outcomes were diarrhoea, nausea, and vomiting. We calculated the relative risk (RR) and 95% confidence interval (CI) for all outcomes. Statistical heterogeneity was calculated using the I^2 statistic.

Results: We included five RCTs (7540 participants) from 7237 citations. Most (80%) were of an unclear to high risk of bias. There was no evidence of a significant improvement with remdesivir (100 mg, 10 days) regarding all-cause mortality (RR 0.94, CI 0.82–1.07; $I^2 = 0\%$; 4 RCTs; 7143 patients), clinical progression (RR 1.08, CI 0.99–1.18; $I^2 = 70.4\%$; 3 RCTs; 1692 patients), or diarrhoea (RR 0.82, CI 0.40–1.66; $I^2 = 0\%$; 2 RCTs; 630 patients). Nausea occurred more often with remdesivir (RR 2.77, CI 1.28–6.03; $I^2 = 0\%$; 2 RCTs; 630 patients). TSA showed that the required information size was not reached for firm conclusions to be drawn.

Conclusions and relevance: There is insufficient evidence to support the use of remdesivir for treatment of COVID-19. More high-quality RCTs are needed for a stronger evidence. Until then, remdesivir should remain an experimental drug for COVID-19.



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Introduction

It has been widely suggested that some antiviral drug formulations for diseases like Ebola and influenza may be effective against COVID-19 [1,2]. In February 2020, the WHO announced a list of pre-existing drugs that could be repurposed for the potential treatment of COVID-19, including two antiviral drugs, remdesivir and lopinavir [3].

Remdesivir is a prodrug that has a broad antiviral activity spectrum among ribonucleic acid (RNA) viruses, including the SARS-CoV-2, and acts by inhibiting RNA polymerase limiting viral replication [4,5]. *In vivo* studies have suggested that remdesivir has therapeutic and prophylactic effects in animal models of SARS-CoV-2 [4], and significantly reduced pulmonary damage has been observed in the early use of the drug on COVID-19 monkeys [6]. Reductions in time to recovery of hospitalized COVID-19 patients who required supplemental oxygen have also been observed in humans [7], with suggestions that the drug may have a positive effect on mortality while also having a good safety profile [4]. However, remdesivir failed in clinical trials on Ebola virus disease for which it was originally formulated [8], necessitating a careful assessment of the drug for the treatment of COVID-19, having been approved for the treatment of severe hospitalized patients at least 12 years old and weighing, at least, 40 kg [9].

The WHO recommended the evaluation of potential drugs through large multinational adaptive randomized controlled trials (RCTs) [10]. Remdesivir became the first approved drug by the United States of America (USA) Food and Drug Administration (FDA) for the treatment of patients with COVID-19 requiring hospitalization [9]. The approval was based on the findings from a multicenter global study that showed that, compared with placebo, it shortened the time to recovery by five days in hospitalized patients [7]. Later, an interim report from another multicenter global study in hospitalized COVID-19 patients led by the WHO reported conflicting results; concluding that there was no difference in mortality between remdesivir and usual clinical care [11]. Smaller RCTs have also assessed remdesivir for COVID-19 with varied findings; thus, necessitating a detailed assessment of all currently available evidence from RCTs.

In view of the accumulating evidence and still many unanswered clinical questions, we systematically identified, critically appraised, and summarised the findings from RCTs of remdesivir for treatment of COVID-19, focussing on clinically relevant outcomes.

Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020216817) and was conducted in accordance to the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines [12]. The findings of this review are reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13].

Search strategy

A literature search strategy for Embase (Ovid) was designed by a knowledge synthesis librarian and peer-reviewed by another independent knowledge synthesis librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist [14]. The search strategy was designed to capture all antiviral treatments and was filtered for randomized controlled trials. The revised search strategy for Embase (Supplementary Table 1) was adopted by the knowledge synthesis librarian for Web of Science Core Collection (Thomson Reuters), LitCovid [15], the Cochrane COVID-19 study register [16], and the World Health Organisation's Global research on coronavirus disease (WHO COVID-19) online database [17]. In addition, the following websites were searched for links to additional peer-reviewed and published literature: ClinicalTrials.gov, the Centres for Disease Control and Prevention (CDC), The Canadian Agency for Drugs and Technologies in Health (CADTH), and The European Centre for Disease Prevention and Control (ECDC). The literature search was conducted on 10 September 2020 (11th September for the CDC, CADTH, and ECDC) and all retrieved literature citations were imported into, and de-duplicated in EndNote citation management software, version X9.

Selection criteria

The de-duplicated citations were imported and screened in a specially designed Microsoft Access 2016 database (Microsoft Corporation, Redmond, WA, USA) by two independent systematic reviewers using a two-stage sifting approach to review the title/abstract and full-text articles of relevant citations. We documented the number of ineligible citations at the title/abstract screening stage, and both the number and reasons for ineligibility at the full-text article screening stage. The two reviewers resolved any disagreements through discussion or involvement of a third reviewer, as needed. We focussed

on RCTs of remdesivir compared with placebo or no treatment or with a different regimen of remdesivir for treatment of laboratory-confirmed (RT-PCR or antigen test) COVID-19 irrespective of disease severity. Our review was restricted to studies on the efficacy and safety of remdesivir for treatment of COVID-19, and we limited to studies published in the English language. We excluded preprint articles.

Our efficacy outcomes were all-cause mortality, viral burden (determined from testing upper respiratory tract specimens including nasopharyngeal and deep nasal swabs, or throat swabs), and clinical progression measured using the WHO scale. For clinical progression, we dichotomized the individual scores ≤ 5 (hospitalized: moderate disease or ambulatory: mild disease) [18] between intervention and comparator groups at the longest follow-up. If measured by a scale other than the WHO scale, we re-classified the measurement according to the WHO criteria. Our safety outcomes were diarrhoea, nausea, and vomiting.

Data extraction

Two reviewers independently extracted data from the included studies using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). We extracted study information, study population characteristics, information regarding interventions and comparators, outcomes assessed, and study results based on an intention-to-treat (ITT) analysis. We also extracted details relevant to the risk of bias assessment. The reviewers independently assessed the risk of bias in the included studies using the Cochrane risk of a bias assessment tool for RCT v2.0.2 [19]. Disagreements were resolved through discussion or by the involvement of a third reviewer, as needed.

Data synthesis and analysis

We synthesized the characteristics of the included studies and the risk of bias assessments in a tabular form. Where possible (when data was available from at least two trials), we conducted a meta-analysis using an inverse variance, random-effects models implemented in STATA (version 13; StataCorp LP, Texas, USA) using the longest follow-up data. Pooled estimates of effects were calculated using relative risk (RR) and the estimates reported with their associated 95% confidence intervals (CIs). We assessed statistical heterogeneity between the pooled estimates using the I^2 statistic [20]. Publication

bias was not assessed because of small sample sizes (<10 study results contributed to the pooled analyses) [21].

To mitigate the potential for type I or type II errors in meta-analysis and to understand if the required information size (total sample size) was attained, we conducted a trial sequential analysis (TSA) for the efficacy outcomes. We used the TSA software (v.0.9.5.5 beta Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark [www.ctu.dk/tsa]) and followed the methods outlined by Wetterslev and colleagues [22]. We used a random-effects model with a conventional test boundary of $p < .05$ and calculated the required information size for efficacy outcomes of remdesivir, utilizing a minimum relative risk reduction of 0.10. For information size calculations, we assumed two-sided tests of significance, a power level of 80%, alpha <0.05 , and adjusted by between-study heterogeneity.

Results

From 7237 citations identified by the search strategy, five RCTs met our eligibility criteria (Figure 1) [7,11,23–25]. The characteristics of these trials are summaries in Table 1 and Supplementary Table 2. All the RCTs were multicenter trials (ranging from 10 to 405 centres), and all but one RCT (conducted only in China) [25] were multinational trials. Two trials were double-blinded [7,25], and the rest were open-label. Two trials (both open-label) were funded by Gilead Sciences, a pharmaceutical company that produces remdesivir [23,24], and the other trials (including the largest two) were non-industry funded.

Patients' inclusion criteria, COVID-19 severity and definition of severity differed across trials. However, the median number of days from symptom onset among patients to being enrolled in the trials were considerably similar (one study did not report this information) [11]. Overall, the number of patients in the trials, irrespective of the intervention arm, ranged from 237 patients to 11,266 patients, with a considerably similar proportion of male patients across all but one trial [25]. All the trials assessed 100 mg remdesivir over 10 days of treatment, and the two industry-funded trials assessed 100 mg remdesivir over 5 days of treatment. One trial, in addition to assessing remdesivir also assessed other interventions [11].

Four trials measured clinical progression outcome; two (the industry-funded) using a 7-category ordinal scale [23,24], and one, 8-category ordinal scale [7], and

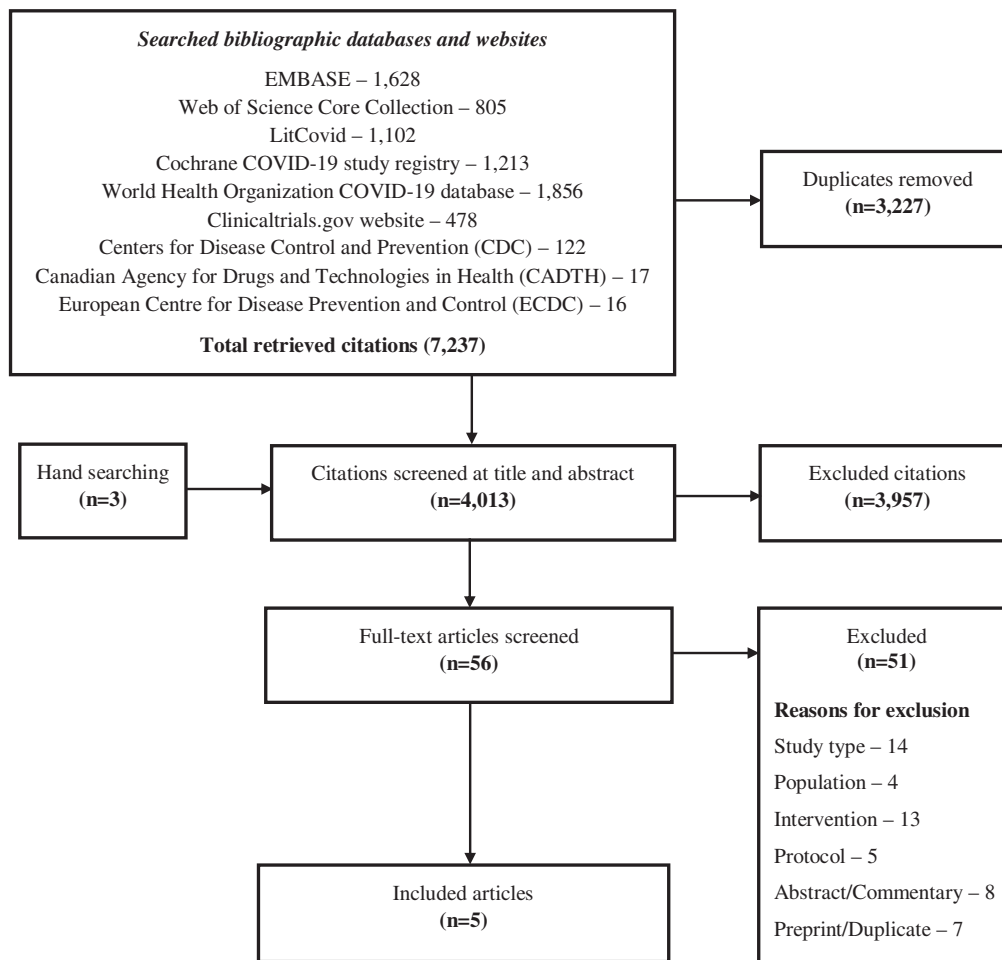


Figure 1. Modified PRISMA flow chart.

the other, 6-category ordinal scale [25]. The longest follow-up time varied across the trials. Overall, one trial was judged to be at low risk of bias [25], two trials judged to be of some concern of risk of bias [7,11], and two trials (the industry-funded) were judged to be at a high risk of bias [23,24] (Figure 2).

Remdesivir (100 mg – 10 days) versus no treatment/placebo

There was no evidence that remdesivir significantly reduced all-cause mortality (RR 0.94, 95% CI 0.82–1.07; $I^2 = 0\%$; 4 RCTs; 7143 patients) or clinical progression (RR 1.08, 95% CI 0.99–1.18; $I^2 = 70.4\%$; 3 RCTs; 1692 patients) (Figure 3). While there was no evidence that remdesivir was associated with an increased risk of developing diarrhoea (RR 0.82, 95% CI 0.40–1.66; $I^2 = 0\%$; 2 RCTs; 630 patients) (Supplementary Figure 1) or vomiting (RR 1.00, 95% CI 0.19–5.34; 1 RCT, 237 patients), there was significantly more nausea (RR 2.77, 95% CI 1.28–6.03; $I^2 = 0\%$; 2 RCTs; 630 patients)

(Supplementary Figure 2) in patients receiving the intervention. No trial reported on viral burden.

Remdesivir (100 mg – 5 days) versus no treatment/placebo

Similar to the 10-day regimen, there was no evidence that a 5-day course of remdesivir significantly reduced all-cause mortality (RR 0.52, 95% CI 0.10–2.83; 1 RCT, 391 patients) or diarrhoea (RR 0.90, 95% CI 0.43–1.89; 1 RCT; 391 patients), but was associated with significantly improved clinical progression (RR 1.05, 95% CI 1.01–1.10; 1 RCT, 391 patients) and nausea (RR 3.32, 95% CI 1.35–8.12; 1 RCT, 391 patients). No trial reported on viral burden or vomiting.

Remdesivir (100 mg – 10 days) versus (100 mg – 5 days)

There was no evidence that remdesivir regimens (100 mg – 10 days vs 5 days) were significantly different in preventing all-cause mortality (RR 1.48, 95% CI

Table 1. Summary of the characteristics of the included Randomised Controlled Trials.

Article (Report type)	Country [Centres]	Blinding (Funding)	COVID-19 severity [Mean/ median symptom onset (days)]	No. of patients (% Male)	Mean (SD)/ median (IQR) age (years)	Interventions (dose – days)	Outcomes (Time to measurement)
Beigel 2020 [7]	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore [73 centres]	Double-blinded (Non-Pharma funded)	Mixed severity [9 (IQR 6–12)]	1062 (64.4%)	58.9 (15)	Remdesivir (100 mg – 10 days) vs. Placebo	All-cause mortality (29 days); clinical progression [eight-category ordinal scale] (15 days)
Goldman 2020 [23]	USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan [55 centres]	Open-label (Gilead Sciences)	Mixed severity [8.5 (IQR 6.4–10.6)]	397 (63.7%)	61.4 (IQR 54.4–68.5)	Remdesivir (100 mg – 10 days) vs. Remdesivir (100 mg – 5 days)	Clinical progression [seven-category ordinal scale] (14 days); nausea (30 days)
Spinner 2020 [24]	USA, Europe, Asia [105 centres]	Open-label (Gilead Sciences)	Moderately severe [8.4 (IQR 6.6–10)]	596 (61.1%)	NR	Remdesivir (100 mg – 10 days) vs. Remdesivir (100 mg – 5 days) vs. No treatment	Clinical progression [seven-category ordinal scale], nausea, diarrhoea (11 days); all-cause mortality (28 days)
Wang 2020 [25]	China [10 centres]	Double-blinded (Non-Pharma funded)	Severe [≤12 days]	237 (56%)	65 (IQR 56–71)	Remdesivir (100 mg – 10 days) vs. Placebo	All-cause mortality, clinical progression [six-category ordinal scale], nausea, diarrhoea, vomiting (28 days)
WHO Solidarity Trial Consortium* 2020 [11]	30 Countries [405 centres]	Open-label (Non-Pharma funded)	Mixed severity [NR]	11,266 (62%)	NR	Remdesivir (100 mg – 10 days) vs. No treatment	All-cause mortality (28 days)

* Interim results.

IQR: interquartile range; SD: standard deviation; NR: not reported; WHO: World Health Organization; vs.: versus; USA: United States of America; UK: United Kingdom.

0.25–8.78; 1 RCT; 384 patients), clinical progression (RR 0.93 95% CI 0.67–1.29; $I^2 = 96.5%$; 2 RCTs; 781 patients), diarrhoea (RR 0.82 95% CI 0.37–1.86; 1 RCT, 384 patients) or nausea (RR 0.90, 95% CI 0.58–1.39; $I^2 = 0%$; 2 RCTs; 781 patients) (Supplementary Figures 3 and 4). No trial reported on viral burden, and vomiting.

Trial sequential analysis

Due to the scant data available, we were only able to conduct TSA for all-cause mortality and clinical progression with remdesivir (100 mg – 10 days) versus no treatment/placebo. Overall, based on a RR reduction of 10%, the sample heterogeneity ($I^2 = 0%$) and an 11% baseline risk of all-cause mortality, the required information size ($n = 24,281$) was not reached (Figure 4). We are therefore unable to conclude whether remdesivir is associated with clinically significant reduction of all-cause mortality.

For clinical progression, based on the RR increase of 9.9% and the sample heterogeneity ($I^2 = 70%$), the required information size ($n = 7,048$) was not reached (Figure 4). We are therefore unable to conclude whether remdesivir is associated with a clinically significant increase of clinical progression of COVID-19.

Ongoing RCTs

We identified in ClinicalTrials.gov website, five ongoing RCTs of remdesivir compared with placebo or no treatment for the treatment of COVID-19. Relevant information regarding these trials is presented in Supplementary Table 3.

Discussion

Based on the current evidence, there is no significant difference between remdesivir and no treatment/placebo for treatment of COVID-19, and the former carries a higher risk of nausea. Furthermore, there is no difference between 10-day and 5-day courses of remdesivir with regard to clinical progression and risk of nausea. We advise cautious interpretations of these findings in view of the paucity of the available evidence and some concern to high risk of bias in a majority of the included trials.

The definition of COVID-19 severity varied significantly across the trials (Supplementary Table 2). For example, while in one trial severity was if patients required mechanical ventilation and supplemental oxygen, with oxygen

Article	Intervention	Comparator	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall assessment
Beigel 2020 [7]	Remdesivir (100mg – 10days)	Placebo	!	+	+	+	+	!
Goldman 2020 [23]	Remdesivir (100mg – 10days)	Remdesivir (100mg – 5days)	-	-	+	!	+	-
Spinner 2020 [24]	Remdesivir (100mg – 10days)	No treatment; Remdesivir (100mg – 5days)	+	-	!	+	+	-
Wang 2020 [25]	Remdesivir (100mg – 10days)	Placebo	+	+	+	+	+	+
WHO Solidarity Trial Consortium 2020 [11]	Remdesivir (100mg – 10days)	No treatment	!	+	+	!	+	!

+ Low risk
! Some concern
- High risk

Figure 2. Risk of bias assessments. WHO: World Health Organization

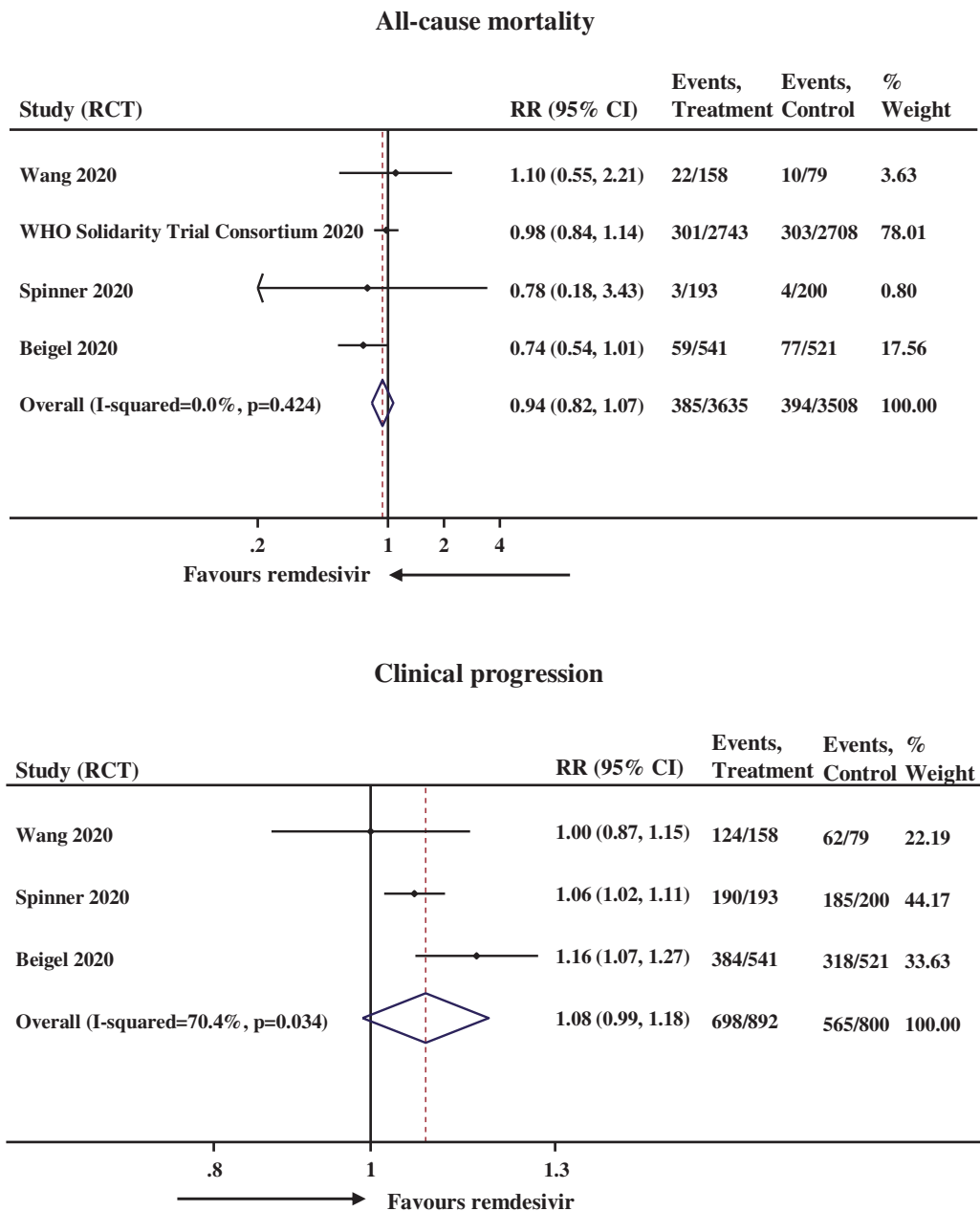
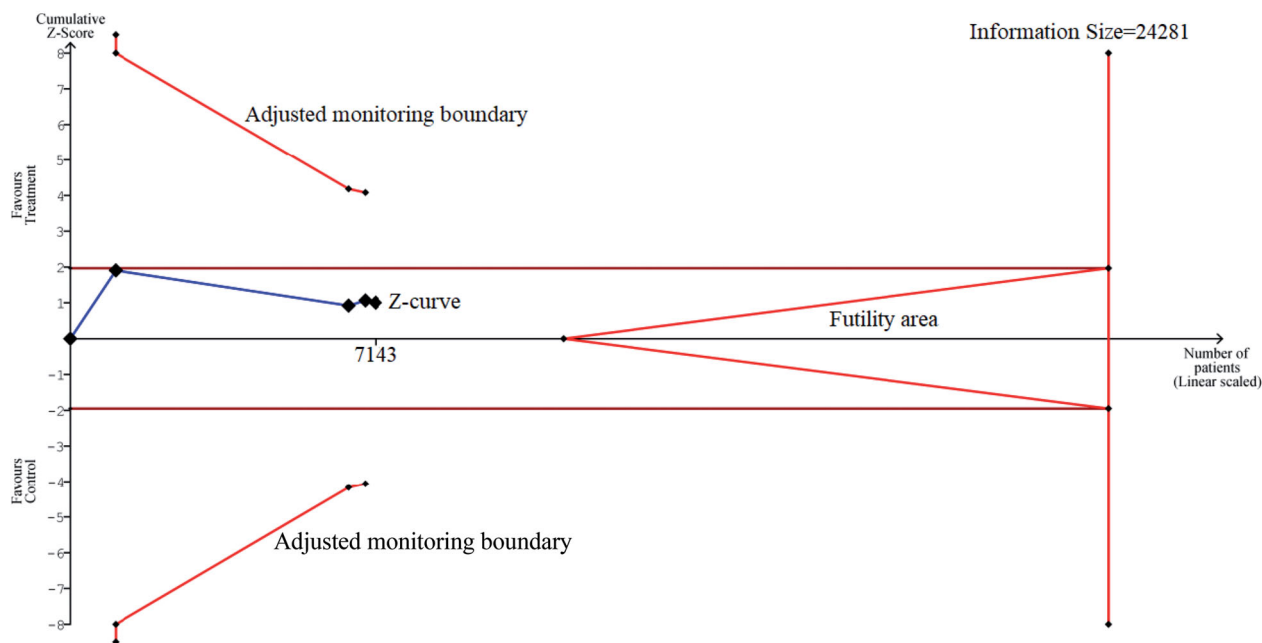


Figure 3. Meta-analysis (remdesivir (100 mg – 10 days) versus no treatment/placebo). WHO: World Health Organization.

All-cause mortality



Clinical progression

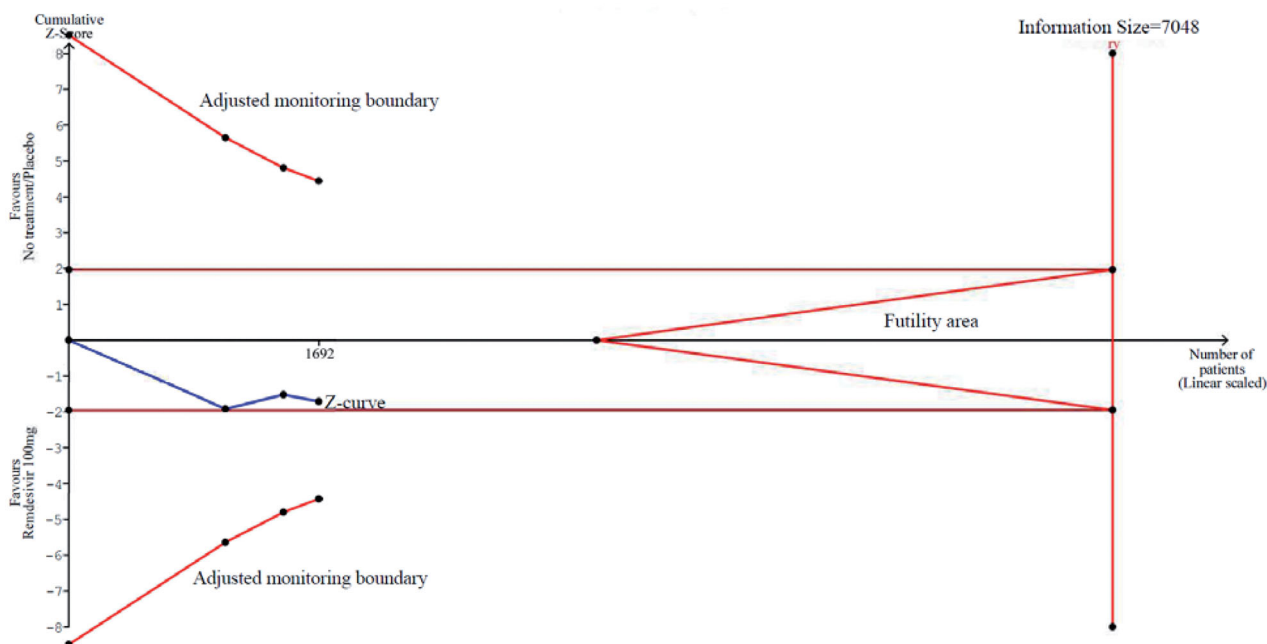


Figure 4. Trial sequential analysis.

saturation of $\leq 94\%$ [7], two other trials defined severe patients to be those who had pneumonia confirmed by chest imaging and having an oxygen saturation of $\leq 94\%$ [24,25]. In another trial, severe patients were simply those ventilated when randomized [11], and severity was not defined explicitly in one trial [23]. Inclusion criteria also varied across studies, with a variable number of days from symptom onset to enrolment, and the minimum age for

enrolment (≥ 12 years in two trials and ≥ 18 years in three trials) although only laboratory-confirmed COVID-19 patients were enrolled in all the trials. It was not clear to what extent the patient populations differed by comorbidity status and the impact that the differences may have made on the trials.

Varied scales were used for assessment of clinical progression across the studies, but the scales were

comparable, allowing us to compare patients that were still hospitalized with moderate disease or were ambulatory with the mild disease at the end of follow-up, between intervention and comparator groups, irrespective of the scale used in the assessment. However, the outcome assessment follow-up period varied across the trials: 11–28 days.

Similar conclusions to those in this review were also reached by a recent systematic review of the efficacy and safety of remdesivir for COVID-19 although the outcomes assessed were different from this review except for all-cause mortality [26]. The review also reported that time to recovery, need for invasive ventilation, and varied pharmacokinetic adverse effect outcomes were similar between remdesivir and the control groups.

This review has some limitations including the paucity of available evidence. We did not search Chinese databases and therefore may have missed potentially eligible trials for inclusion. However, the searched databases, in particular, the COVID-19 curated databases, are the most comprehensive resources on the topic and represent comprehensive multilingual sources of current up-to-date literature on COVID-19. Similarly, limiting the included trials in this review to only those published in the English language meant that any potentially eligible non-English publications would have been excluded. However, considering the global spread and menace of COVID-19 and the need to quickly disseminate easily accessible information globally, it is likely that trials originally reported in languages other than English would have also been reported in English. Furthermore, it is not clear to what extent our deduction of clinical progression outcome from varied clinical progression measurement scales impacted our findings, especially considering that none of the scales conveyed an established minimum clinically important difference or was validated. In addition, a higher proportion of remdesivir recipients than placebo recipients had dosing prematurely stopped by the investigators because of adverse events in one trial [25], and it is not clear to what extent this might have impacted the findings.

This review has many merits, including utilization of the expertise of knowledge synthesis librarians in developing a comprehensive search strategy, peer review of the search strategy using a validated checklist and searching appropriate databases for literature. We adhered to known guidelines and standards in the conduct and reporting of the review. In addition, a consistent remdesivir dosing was used across the included trials although a couple of the trials also assessed

alternative dosing. Finally, the findings answer some clinical questions that contribute significantly to the evidence base to help clinicians and policymakers in decision-making regarding the treatment of COVID-19 with remdesivir, and highlights the need for more trials.

Although there are clinical and ethical reasons for patients not to be denied any symptomatic and potentially life-saving drugs across the trials and depending on local practices, allowing such unbalanced administration of other drugs means that the specific efficacy and safety of remdesivir may never be determined. It is also possible that differences in the timing of intervention start relative to symptom onset and differences in follow-up periods will have impacted the findings from this review although this would be difficult to determine with certainty.

Conclusions

Despite the approval of remdesivir for use in hospitalized severe COVID-19 patients, the available evidence suggests that daily treatment with 100 mg remdesivir over 10 days is not better than no treatment/placebo. More high-quality RCTs are therefore needed for a stronger evidence base.

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Author contributions

Conceptualization (GN Okoli & AM Abou-Setta); Methodology (GN Okoli, R Rabbani & AM Abou-Setta); Data acquisition (GN Okoli, L Copstein, A Al-Juboori, N Askin, & AM Abou-Setta); Formal analysis (GN Okoli & R Rabbani); Validation (GN Okoli, R Rabbani & AM Abou-Setta); Draft manuscript (GN Okoli); Manuscript revisions (GN Okoli, R Rabbani, L Copstein, A Al-Juboori, N Askin & AM Abou-Setta); Final approval for submission (GN Okoli, R Rabbani, L Copstein, A Al-Juboori, N Askin & AM Abou-Setta); Accountability (GN Okoli, R Rabbani, L Copstein, A Al-Juboori, N Askin & AM Abou-Setta)

Disclosure statement

No potential conflict of interest was reported by the author(s).

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