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Remdesivir for the treatment of COVID-19 (Review)

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[Intervention Review]

Remdesivir for the treatment of COVID-19

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ABSTRACT

Background

Remdesivir is an antiviral medicine with properties to inhibit viral replication of SARS-CoV-2. Positive results from early studies attracted media attention and led to emergency use authorisation of remdesivir in COVID-19. A thorough understanding of the current evidence regarding the effects of remdesivir as a treatment for SARS-CoV-2 infection based on randomised controlled trials (RCTs) is required.

Objectives

To assess the effects of remdesivir compared to placebo or standard care alone on clinical outcomes in hospitalised patients with SARS-CoV-2 infection, and to maintain the currency of the evidence using a living systematic review approach.

Search methods

We searched the Cochrane COVID-19 Study Register (which comprises the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and medRxiv) as well as Web of Science (Science Citation Index Expanded and Emerging Sources Citation Index) and WHO COVID-19 Global literature on coronavirus disease to identify completed and ongoing studies without language restrictions. We conducted the searches on 16 April 2021.

Selection criteria

We followed standard Cochrane methodology.

We included RCTs evaluating remdesivir for the treatment of SARS-CoV-2 infection in hospitalised adults compared to placebo or standard care alone irrespective of disease severity, gender, ethnicity, or setting.

We excluded studies that evaluated remdesivir for the treatment of other coronavirus diseases.

Data collection and analysis

We followed standard Cochrane methodology.

To assess risk of bias in included studies, we used the Cochrane RoB 2 tool for RCTs. We rated the certainty of evidence using the GRADE approach for outcomes that were reported according to our prioritised categories: all-cause mortality at up to day 28, duration to liberation from invasive mechanical ventilation, duration to liberation from supplemental oxygen, new need for mechanical ventilation (high-flow oxygen, non-invasive, or invasive mechanical ventilation), new need for invasive mechanical ventilation, new need for non-invasive mechanical ventilation or high-flow oxygen, new need for oxygen by mask or nasal prongs, quality of life, serious adverse events, and adverse events (any grade).

Main results

We included five RCTs with 7452 participants diagnosed with SARS-CoV-2 infection and a mean age of 59 years, of whom 3886 participants were randomised to receive remdesivir. Most participants required low-flow oxygen (n=4409) or mechanical ventilation (n=1025) at baseline. Studies were mainly conducted in high- and upper-middle-income countries. We identified two ongoing studies, one was suspended due to a lack of COVID-19 patients to recruit.

Risk of bias assessments were considered to be some concerns or high risk for clinical status and safety outcomes because participants who had died did not contribute information to these outcomes. Without adjustment, this leads to an uncertain amount of missing values and the potential for bias due to missing data.

Effects of remdesivir in hospitalised individuals

Remdesivir probably makes little or no difference to all-cause mortality at up to day 28 (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.81 to 1.06; risk difference (RD) 8 fewer per 1000, 95% CI 21 fewer to 7 more; 4 studies, 7142 participants; moderate-certainty evidence). There was limited evidence for a beneficial effect of remdesivir on mortality in a subset of 435 participants who received low flow oxygen at baseline in one study (RR 0.32, 95% CI 0.15 to 0.66). We could not confirm this finding due to restricted availability of relevant subgroup data from other studies.

Remdesivir may have little or no effect on the duration to liberation from invasive mechanical ventilation (2 studies, 1298 participants, data not pooled, low-certainty evidence). We are uncertain whether remdesivir increases or decreases the chance of clinical improvement in terms of duration to liberation from supplemental oxygen at up to day 28 (3 studies, 1691 participants, data not pooled, very low-certainty evidence).

We are very uncertain whether remdesivir decreases or increases the risk of clinical worsening in terms of new need for mechanical ventilation at up to day 28 (high-flow oxygen or non-invasive ventilation or invasive mechanical ventilation) (RR 0.78, 95% CI 0.48 to 1.24; RD 29 fewer per 1000, 95% CI 68 fewer to 32 more; 3 studies, 6696 participants; very low-certainty evidence); new need for non-invasive mechanical ventilation or high-flow oxygen (RR 0.70, 95% CI 0.51 to 0.98; RD 72 fewer per 1000, 95% CI 118 fewer to 5 fewer; 1 study, 573 participants; very low-certainty evidence); and new need for oxygen by mask or nasal prongs (RR 0.81, 95% CI 0.54 to 1.22; RD 84 fewer per 1000, 95% CI 204 fewer to 98 more; 1 study, 138 participants; very low-certainty evidence). Remdesivir may decrease the risk of clinical worsening in terms of new need for invasive mechanical ventilation (67 fewer participants amongst 1000 participants; RR 0.56, 95% CI 0.41 to 0.77; 2 studies, 1159 participants; low-certainty evidence).

None of the included studies reported quality of life.

Remdesivir probably decreases the serious adverse events rate at up to 28 days (RR 0.75, 95% CI 0.63 to 0.90; RD 63 fewer per 1000, 95% CI 94 fewer to 25 fewer; 3 studies, 1674 participants; moderate-certainty evidence). We are very uncertain whether remdesivir increases or decreases adverse events rate (any grade) (RR 1.05, 95% CI 0.86 to 1.27; RD 29 more per 1000, 95% CI 82 fewer to 158 more; 3 studies, 1674 participants; very low-certainty evidence).

Authors' conclusions

Based on the currently available evidence remdesivir probably has little or no effect on all-cause mortality at up to 28 days in hospitalised adults with SARS-CoV-2 infection. We are uncertain about the effects of remdesivir on clinical improvement and worsening. There were insufficient data available to examine the effect of remdesivir on mortality across subgroups defined by respiratory support at baseline.

Future studies should provide additional data on efficacy and safety of remdesivir for defined core outcomes in COVID-19 research, especially for different population subgroups. This could allow us to draw more reliable conclusions on the potential benefits and harms of remdesivir in future updates of this review. Due to the living approach of this work, we will update the review periodically.

PLAIN LANGUAGE SUMMARY

Remdesivir to treat people with COVID-19

Is remdesivir (an antiviral medicine) an effective treatment for COVID-19?

Key messages

• For adults hospitalised with COVID-19, remdesivir probably has little or no effect on deaths from any cause up to 28 days after treatment compared with placebo (sham treatment) or usual care.

• We are uncertain whether remdesivir improves or worsens patients' condition, based on whether they needed more or less help with breathing.

• Researchers should agree on key outcomes to be used in COVID-19 research, and future studies should investigate these areas. This would allow future updates of this review to draw more certain conclusions about the use of remdesivir to treat COVID-19.

What is remdesivir?

Remdesivir is a medicine that fights viruses. It has been shown to prevent the virus that causes COVID-19 (SARS-CoV-2) from reproducing. Medical regulators have approved remdesivir for emergency use to treat people with COVID-19.

What did we want to find out?

We wanted to know if remdesivir is an effective treatment for people in hospital with COVID-19 and if it causes unwanted effects compared to placebo or usual care.

People with COVID-19 are given different kinds of breathing support, depending on how severe their breathing difficulties are. We used the types of breathing support people received as a measure of the success of remdesivir in treating COVID-19. Types of breathing support included:

• for severe breathing difficulties: invasive mechanical ventilation, when a breathing tube is put into patients' lungs, and a machine (ventilator) breathes for them. Patients are given medicine to make them sedated whilst they are on a ventilator.

• for moderate to severe breathing difficulties: non-invasive mechanical ventilation through a mask over the nose and/or mouth, or a helmet. Air or oxygen is pushed through the mask. Patients are generally awake for this treatment.

• for moderate breathing difficulties: oxygen via a mask or prongs that sit in the nostrils. Patients can still breathe room air.

We were interested in the following outcomes:

• deaths from any cause in the 28 days after treatment;

• whether patients got better after treatment, measured by how long they spent on mechanical ventilation or oxygen;

• whether patients' condition worsened so that they needed oxygen or mechanical ventilation;

• quality of life;

• any unwanted effects; and

• serious unwanted effects.

What did we do?

We searched for studies that investigated remdesivir to treat adults with COVID-19 compared to placebo or standard care. Patients were hospitalised with COVID-19 and could be of any gender or ethnicity.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 5 studies with 7452 people hospitalised with COVID-19. Of these, 3886 people were given remdesivir. The average age of patients was 59 years. Studies took place around the world, mainly in high- and upper-middle-income countries.

Main results

The included studies compared remdesivir to placebo or usual care in people hospitalised with COVID-19 for up to 28 days.

Deaths from any cause

• Remdesivir probably makes little or no difference to deaths from any cause (4 studies, 7142 people). In 1000 people, 8 fewer die with remdesivir compared to placebo or standard care.

Did patients get better with remdesivir?

• Remdesivir may have little or no effect on the length of time patients spent on invasive mechanical ventilation (2 studies, 1298 people).

• We do not know whether remdesivir increases or decreases time on supplemental oxygen (3 studies, 1691 people).

Did patients get worse with remdesivir?

• We do not know whether patients are more or less likely to need any mechanical ventilation (invasive or non-invasive) with remdesivir (3 studies, 6696 people).

• Patients may be less likely to need invasive mechanical ventilation (2 studies, 1159 people).

• We do not know whether patients are more or less likely to need non-invasive mechanical ventilation (1 study, 573 people).

• We do not know whether patients are more or less likely to need oxygen by mask or nasal prongs (1 study, 138 people).

Quality of life

• None of the included studies reported quality of life.

Unwanted effects

• We do not know whether remdesivir leads to more or fewer unwanted effects of any level (3 studies, 1674 people).

• Patients are probably less likely to experience serious unwanted effects with remdesivir than with placebo or standard care (3 studies, 1674 people). In 1000 people, 63 fewer would experience a serious unwanted effect compared to placebo or standard care.

What are the limitations of the evidence?

We are moderately confident in the evidence for deaths from any cause and serious unwanted effects; however, our confidence in the other evidence is limited because studies used different methods to measure and record their results, and we did not find many studies for some of our outcomes of interest.

How up-to-date is this evidence?

The evidence is current to 16 April 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Remdesivir compared to placebo or standard care alone for hospitalised adults with confirmed SARS-CoV-2 infection

Remdesivir compared to placebo or standard care alone for hospitalised adults with confirmed SARS-CoV-2 infection

Patient or population: hospitalised adults with confirmed SARS-CoV-2 infection
Settings: in-hospital
Intervention: remdesivir (10 days)
Comparator: placebo or standard care alone

Outcomes	Anticipated absolute effects		Relative effect 95% CI	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk					
	Placebo or standard care alone	Risk difference with remdesivir				
All-cause mortality at up to day 28	108 per 1000[i]	8 fewer per 1000 (21 fewer to 7 more)	RR 0.93 (0.81 to 1.06)	7142 (4 RCTs)	⊕⊕⊕⊖ MODERATE Due to serious imprecision[1]	Remdesivir probably makes little or no difference to all-cause mortality.
Improvement of clinical status: duration to liberation from invasive mechanical ventilation at up to day 28	2 studies reported this outcome as median, which could not be included in meta-analysis. 1 study reported a median of 17 days (IQR 9 to 28) in the remdesivir group and 20 days (IQR 8 to 28) in the control group (rate difference −3.0, 95% CI −9.3 to 3.3). The other study reported a median of 7 days (IQR 4 to 16) in the remdesivir group and 15.5 days (IQR 6 to 21) in the control group (rate difference –4.0, 95% CI –14 to 2).			1298 (2 RCTs)	⊕⊕⊖⊖ LOW Due to serious risk of bias and serious imprecision[2,3]	Remdesivir may have little or no effect on improvement of clinical status: duration to liberation from invasive mechanical ventilation.
Improvement of clinical status: duration to liberation from supplemental oxygen at up to day 28	3 studies reported this outcome as median, which could not be included in meta-analysis. 1 study reported a median of 13 days (IQR 5 to 28) in the remdesivir group and 21.0 days (IQR 8 to 28) in the control group (rate difference −8.0, 95% CI −11.8 to -4.2). 1 study reported a median of 19 days (IQR 11 to 30) in the remdesivir and 21 days (IQR 14 to 30.5) in the control group (rate difference −2, 95% CI −6 to 1). The third study reported time to room air regardless of the initial respiratory support: 4 days (IQR 2 to 6) in the remdesivir group and 6 days (IQR 4 to 14) in the control group (HR 1.93, 95% CI 1.11 to 3.36).			1691 (3 RCTs)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias, serious imprecision, and other considerations[2,4,5]	We are uncertain as to whether remdesivir increases or decreases the chance of clinical improvement: duration to liberation from supplemental oxygen .

Clinical worsening: new need for mechanical ventilation at day 28 (defined as high-flow oxygen, non-invasive, or invasive mechanical ventilation)	131 per 1000	29 fewer per 1000 (68 fewer to 32 more)	RR 0.78 (0.48 to 1.24)	6696 (3 RCTs)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias, serious imprecision, and serious inconsistency[1,4,6]	We are very uncertain as to whether remdesivir decreases or increases the risk of clinical worsening: new need for mechanical ventilation.
Clinical worsening: new need for invasive mechanical ventilation at up to day 28	152 per 1000	67 fewer per 1000 (90 fewer to 35 fewer)	RR 0.56 (0.41 to 0.77)	1159 (2 RCTs)	⊕⊕⊖⊖ LOW Due to serious risk of bias and other considerations[4,5]	Remdesivir may decrease the risk of clinical worsening: new need for invasive mechanical ventilation.
Clinical worsening: new need for non-invasive mechanical ventilation or high-flow oxygen at up to day 28	241 per 1000	72 fewer per 1000 (118 fewer to 5 fewer)	RR 0.70 (0.51 to 0.98)	573 (1 RCT)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias and very serious imprecision[3,7]	We are very uncertain as to whether remdesivir decreases or increases the risk of clinical worsening: new need for non-invasive mechanical ventilation or high-flow oxygen.
Clinical worsening: new need for oxygen by mask or nasal prongs at up to day 28	444 per 1000	84 fewer per 1000 (204 fewer to 98 more)	RR 0.81 (0.54 to 1.22)	138 (1 RCT)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias and very serious imprecision[3,8]	We are very uncertain as to whether remdesivir decreases or increases the risk of clinical worsening: new need for oxygen by mask or nasal prongs.
Quality of life	NA	NA	NA	NA	NA	None of the included studies reported quality of life, therefore we do not know whether remdesivir has any impact on this outcome.
Serious adverse events at up to day 28	253 per 1000	63 fewer per 1000 (94 fewer to 25 fewer)	RR 0.75 (0.63 to 0.90)	1674 (3 RCTs)	⊕⊕⊕⊖ MODERATE Due to serious risk of bias[3]	Remdesivir probably decreases the risk of serious adverse events.
Adverse events (any grade) at up to day 28	587 per 1000	29 more per 1000 (82 fewer to 158 more)	RR 1.05 (0.86 to 1.27)	1674 (3 RCTs)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias, serious inconsistency, and serious imprecision[1,3,9]	We are very uncertain as to whether remdesivir increases or decreases adverse events (any grade).

CI: confidence interval; **HR:** hazard ratio; **IQR:** interquartile range; **NA**: not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

i. All-cause mortality at hospital discharge: RR 0.98, 95% CI 0.84 to 1.14; 1 study, 5451 participants; I^2 not applicable. All-cause mortality (time-to-event): HR 0.93, 95% CI 0.80 to 1.07; 2 studies, 6513 participants; $I^2 = 57\%$.

[1]Downgraded one level due to serious imprecision because of wide confidence intervals in the studies and the 95% confidence interval includes both benefits and harms.

[2]Downgraded one level due to serious imprecision because the 95% confidence interval includes both benefits and harms.

[3]Downgraded one level due to serious risk of bias because of competing risk of death.

[4]Downgraded one level due to serious risk of bias because of inadequate blinding of participants, personnel, and outcome assessors and possible deviation in time point of measuring in one study, and competing risk of death.

[5]Downgraded one level due to other considerations, as studies reported outcomes differently because of missing standards.

[6]Downgraded one level due to serious inconsistency because of statistical heterogeneity ($I^2 = 85\%$).

[7]Downgraded two levels due to serious imprecision because of few participants and data from only one study.

[8]Downgraded two levels due to very serious imprecision because of wide confidence intervals and data from only one study.

[9]Downgraded one level due to serious inconsistency because of statistical heterogeneity ($I^2 = 77\%$).

BACKGROUND

This work is part of a series of Cochrane Reviews investigating treatments and therapies for coronavirus disease 2019 (COVID-19). Reviews of this series share information in the background section and methodology based on the first published reviews about monoclonal antibodies, Kreuzberger 2021, and convalescent plasma (Chai 2020), and are part of the German research project "CEOsys" (COVID-19 Evidence-Ecosystem; CEOsys 2021).

Description of the condition

COVID-19 is a rapidly spreading infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 11 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak as a pandemic (WHO 2020a). COVID-19 is unprecedented to previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS, Table 1), with 813 and 858 deaths, respectively (WHO 2003; WHO 2019). In particular with respect to public health, socio-economic conditions, and severity of the disease, it has surpassed the aforementioned outbreaks. Despite intensive international efforts to contain its spread, as of July 2021, the cumulative number of cases reported globally is almost 200 million, and the number of deaths is more than 4 million (WHO 2020b; WHO 2021a; WHO 2021b).

SARS-CoV-2 is a positive-sense, double-stranded ribonucleic acid (RNA) virus that belongs to the *Coronaviridae* family (Chen 2020; Kumar 2020). There is widespread consensus that SARS-CoV-2 is closely related to a beta coronavirus detected in bat faeces. However, the host of origin and the intermediate host remain unclear (Lundstrom 2020; Malaiyan 2020; WHO 2021c). SARS-CoV-2 binds to angiotensin-converting enzyme 2 receptors, which are expressed in lung, heart, kidney, intestine, as well as endothelium, by means of its spike glycoprotein (Yan 2020). Viral variants mainly present mutational changes in the spike glycoprotein (WHO 2021d). Infection with SARS-CoV-2 results in an immune response involving $CD4^+$ and $CD8^+$ T cells, which may lead to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome through cytokine storm syndrome as a result of the release of pro-inflammatory cytokines and chemokines (Li 2020b).

The median incubation time is estimated at between five and six days, and 97.5% of symptomatic cases develop symptoms within 11.5 days of exposure (Lauer 2020). Signs and symptoms can include sore throat, cough, fever, headache, fatigue, and myalgia or arthralgia. The presence of anosmia and ageusia, with an overall low sensitivity (lower than 50%), has a specificity greater than 90% and may be useful as a red flag for COVID-19 (Struyf 2021). Other symptoms include shortness of breath, chills, nausea or vomiting, diarrhoea, nasal congestion, haemoptysis, and conjunctival congestion (WHO 2020c).

A large proportion of infected individuals remain asymptomatic throughout the course of the disease, depending on the time of the investigation, the cohort investigated, and the dominant circulating virus variants (Chen 2020a; Pan 2020; Wu 2020; Funk 2021). The reported frequency of asymptomatic courses also varies greatly and ranges between 6% and 96% (Oran 2020; Funk 2021). In a meta-analysis, Buitrago-Garcia and colleagues estimated the proportion of persistently asymptomatic infected individuals at 20%, with a prediction interval of 3% to 67% (Buitrago-Garcia 2020). Despite the absence of clinical signs, asymptomatic individuals show typical findings on chest computed tomography (CT) in up to 50% of cases (Hu 2020; Meng 2020).

A smaller proportion of infected individuals are affected by severe (approximately 11% to 20%) or critical (approximately 1% to 5%) disease with hospitalisation and intensive care unit (ICU) admittance due to respiratory failure, septic shock, or multiple organ dysfunction syndrome (Wu 2020; Funk 2021). In a case series from 12 New York hospitals, 14% of patients hospitalised due to COVID-19 were treated in ICU (Richardson 2020). Evaluations of patients during the first COVID-19 wave in Germany show an estimate of 14% to 37% of this proportion (Schilling 2020; Tolksdorf 2020). In an observational study of 10,021 hospitalised adult patients in Germany with a confirmed COVID-19 diagnosis, 17% received mechanical ventilation (non-invasive and invasive). In this study, 27% of ventilated patients required dialysis due to acute renal failure. Mortality in patients not receiving mechanical ventilation was 16%, and up to 53% in ventilated patients. Mortality in patients receiving mechanical ventilation (non-invasive and invasive) and dialysis was 73% (Karagiannidis 2020). In a systematic review and meta-analysis of international studies, the proportion of patients who died was estimated at 34% amongst those treated in ICU, and 83% amongst those receiving invasive mechanical ventilation (Potere 2020).

The infection fatality ratio varies widely between countries and reporting periods (from 0.01% to more than 25%). However, these numbers may be misleading as they tend to overestimate the infection fatality ratio due to varying testing frequency, lag in reporting dates, and variations in case definitions, especially in the beginning of the pandemic, as clinicians were mainly focused on severe cases (Wu 2020; WHO 2020b).

Risk for severe disease, hospitalisation, and mortality is higher for individuals aged 65 years or older, males, smokers, and individuals with certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart conditions, immunocompromised state, obesity, sickle cell disease, or type 2 diabetes mellitus (Huang 2020; Karagiannidis 2020; Liang 2020; Petrilli 2020; WHO 2020c; Williamson 2020a).

Vaccination has been shown to be highly effective at reducing severe illness and death from COVID-19. As of July 2021, more than 2.95 billion doses of COVID-19 vaccines have been administered at the global level (https://covid19.who.int/). However, the majority of vaccines have been administered in a few high-income countries. The majority of the world's population still remains susceptible to SARS-CoV-2 infection and at risk of developing COVID-19. Moreover, the duration and degree of protection against the disease, but also against infection and transmission, is still not well-defined, and vaccine hesitancy poses direct and indirect threats to health (Grubaugh 2020). Besides unequal access to vaccines, there is evidence indicating a significant impact of certain circulating variants of SARS-CoV-2 on immunity that is likely to have an impact on the epidemiological situation. (Grubaugh 2020; Schwarz 2021).

In light of the extent of the pandemic, including evolving virus variants and a scarcity of effective treatments as well as issues related to the global availability of vaccines, the role of effective therapies is of utmost interest for combating COVID-19.

Description of the intervention

Remdesivir (GS-5734) is an antiviral agent derived from a small-molecule library and designed to target the replication of pathogenic RNA viruses (Siegel 2017). It evinced a broad-spectrum in vitro efficacy against various emerging viruses, such as *Filoviridae* (e.g. Ebolavirus and Marburgvirus), *Pneumoviridae* (respiratory syncytial virus), and *Coronaviridae* (MERS-CoV, SARS-CoV) (Sheahan 2017; Choy 2020).

In the large and complex 2014 to 2016 outbreak in West Africa, remdesivir showed promising in vivo activity against the Ebola virus (Warren 2016; Tchesnokov 2019). In rhesus monkeys infected with Ebola virus, the novel nucleoside analog led to reduced plasma viral RNA and beneficial impact on clinical progression (Warren 2016). However, when transferred to patients, the remdesivir arm of a randomised controlled trial (RCT) was stopped early due to significant inferiority to monoclonal antibody treatment on mortality (Mulangu 2019).

Sheahan and colleagues outlined the possible relevance of remdesivir in the prevention and treatment of existing and emerging coronaviruses in a mouse model in 2017 (Sheahan 2017). Studies on murine models of SARS infection as well as MERS infection models in rhesus monkeys showed a significant reduction in virus replication, improvement of clinical symptoms, and reduction of lung tissue damage rate (de Wit 2020; Sheahan 2020). In terms of these effects, remdesivir was superior to other antiviral substances such as ribavirin or lopinavir/ritonavir (Sheahan 2020). Two years later, the SARS-CoV-2 pandemic led to rapid investigation of remdesivir as a potential virostatic drug. In vitro testing supported its efficacy against different clinical isolates, partially at low-micromolar concentration (Choy 2020; Ogando 2020; Wang 2020). Early administration in SARS-CoV-2-inoculated macaques reduced respiratory symptoms and lung damage compared to vehicle-treated controls (Williamson 2020b). However, pharmacokinetic data in humans, precisely COVID-19 patients, is rare, and the impact of impaired organ function on drug availability in infected cells is yet not well understood.

During the course of the COVID-19 pandemic, the antiviral agent was initially administered to hospitalised patients with COVID-19 in a compassionate-use attempt. The Adaptive COVID-19 Treatment Trial (ACTT-1) was one of the first multicentre RCTs to report a shortened time to recovery in hospitalised COVID-19 patients compared to standard care (Beigel 2020). Shortly after its publication, the US Food and Drug Administration released an Emergency Use Authorisation on 1 May 2020 (EUA 2021). Based on the recommendation of the European Medicines Agency, the European Union Commission followed in July 2020 with the authorisation of remdesivir as the first treatment option in patients at least 12 years of age with COVID-19 pneumonia and the need for supplementary oxygen (EUA 2020). Later that year, the Committee for Medicinal Products for Human Use narrowed the indication to patients with low- or high-flow oxygen or other non-invasive ventilation (EMA 2020). The recommended dosing regimen is 200 mg intravenously (loading dose), followed by 100 mg over five to 10 days. According to the manufacturer, Gilead Science, phase one clinical trials revealed good tolerability and safety of intravenous administration of remdesivir in healthy individuals (EUA 2021). Reported side effects included phlebitis, constipation, headache, ecchymosis, nausea, and pain in the extremities, as well as transient increase in transaminases, prothrombin time, and blood glucose in laboratory findings (Malin 2020).

Meanwhile, further RCTs relativised the initial euphoria. Amongst them were the interim results of the WHO Solidarity trial, which could not find a benefit for time to clinical improvement, need for mechanical ventilation, or mortality (WHO Solidarity Trial Consortium 2021). Based on a meta-analysis of four RCTs, the WHO updated its COVID-19 treatment guidelines in January 2021 and recommended against the use of remdesivir in hospitalised patients (WHO 2021).

How the intervention might work

Remdesivir (GS-5734) is a mono phosphoramidate nucleoside prodrug which inhibits the synthesis of viral RNA. By competing with its natural analog adenosine triphosphate, it blocks the RNA-polymerase and leads to delayed chain termination, hence inhibiting the virus replication (Siegel 2017). The addition of the monophosphate prodrug improves the intracellular uptake, where phosphorylation turns it into its active metabolite (McGuigan 2006; Lo 2017).

In the early stage of a SARS-CoV-2-associated pneumonia, the reduction of the viral load is postulated to prevent a systemic inflammatory reaction and, in particular, alveolar damage. The clinical presentation of COVID-19 in the late pulmonary phase as well as in the hyper inflammatory phase are dominated by immunological processes, so that antiviral therapy strategies are no longer likely to be effective (Gautret 2020).

In summary, the broad-spectrum nucleoside analog remdesivir could be beneficial in the early stages of SARS-CoV-2-infection by inhibiting virus replication. This hypothesis is supported by promising in vitro and animal experiments (Choy 2020; Wang 2020; Williamson 2020b).

Why it is important to do this review

There is a clear and urgent need for more evidence-based information to guide clinical decision-making for COVID-19 patients. Current treatment consists of supportive care with oxygen supply in moderately severe cases, and non-invasive ventilation or invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) in severe cases (CDC 2020; WHO 2020b). To date, few drugs have been shown to be of clear benefit in the treatment of COVID-19, such as corticosteroids. Few drugs are approved for the treatment of COVID-19, and international guidelines are constantly updated.

The application of remdesivir in COVID-19 patients aims to reduce symptom severity as well as disease progression through inhibited virus replication. Whilst early clinical trials seemed to reproduce positive effects on clinical improvement, leading to widespread authorisation of emergency use, the currently available data are conflicting and uncertain. In part, expectations raised by in vitro findings were not met. Extensive work in the field of systematic reviews for interventions for COVID-19 has already been undertaken, including on remdesivir. Assessment of the available data is not trivial due to inconsistent endpoint definitions, making it difficult to compare conducted trials. One review saw a reduction in mortality (Bansal 2021), whilst other reviews saw no or very small effects on mortality (Piscoya 2020; Siemieniuk 2020; Bhimrai 2021; Vegivinti 2021; Wilt 2021). A similarly inconsistent picture emerges

for clinical improvement and incidence of (serious) adverse events (Elsawah 2020; Yokoyama 2020; Al-Abdouh 2021; Kaka 2021; Wilt 2021).

These differences in the assessment of evidence can be attributed in part to the fact that some reviews also included non-randomised studies (e.g. Bansal 2021). Furthermore, data regarding important subgroups are not readily available.

This systematic review will fill current gaps by identifying, describing, evaluating, and synthesising all evidence for remdesivir on clinical outcomes in COVID-19. There is a need for a thorough understanding and an extensive review of the current body of evidence regarding the use of remdesivir for the treatment of COVID-19. The primary goal of this review is to provide practising clinicians, healthcare providers, and interested laypersons with reliable and evidence-based information that will lead to improvement in the treatment of COVID-19.

OBJECTIVES

To assess the effects of remdesivir compared to placebo or standard care alone on clinical outcomes in hospitalised patients with SARS-CoV-2 infection, and to maintain the currency of the evidence using a living systematic review approach.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on a template from the Cochrane Haematology working group in line with the series of Cochrane Reviews investigating treatments and therapies for COVID-19. We made specific adaptations related to the research question where necessary. The protocol for this review was registered with PROSPERO on 26 February 2021 (CRD42021238065).

To assess the effects of remdesivir for treatment in hospitalised individuals with SARS-CoV-2 infection, we included RCTs, as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly controlled therapeutic settings. We used the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). We had planned to also accept non-standard RCT designs, such as cluster-randomised trials (methods as recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions*) and cross-over trials (Higgins 2021b). We would only have considered results from the first period for cross-over trials, because COVID-19 is not a chronic condition, and its exact course and long-term effects have yet to be defined.

We excluded controlled non-randomised studies of intervention and observational studies. We also excluded animal studies, pharmacokinetic studies, and in vitro studies.

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes.

- Full-text publications
- Preprint articles
- Abstract publications
- Results published in trials registries
- Personal communication with investigators

We included preprints and conference abstracts to have a complete overview of the ongoing research activity, especially for tracking newly emerging studies about remdesivir in COVID-19. We did not apply any limitation with respect to length of follow-up.

Types of participants

We included adults with a confirmed diagnosis of COVID-19 (as described in the study) and did not exclude any studies based on gender, ethnicity, disease severity, or setting.

We excluded studies that evaluated remdesivir for the treatment of other coronavirus diseases such as SARS or MERS, or other viral diseases, such as Ebola. We planned that if studies enrolled populations with or who were exposed to mixed viral diseases, we would only include these if the trial authors provided subgroup data for SARS-CoV-2 infection.

Types of interventions

We included the following interventions:

- Remdesivir for the treatment of SARS-CoV-2 infection.

We included the following comparisons:

- Placebo or standard care alone.

Types of outcome measures

We evaluated core outcomes in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020; WHO 2020d), and additional important outcomes that have been prioritised by consumer representatives and the German guideline panel for inpatient therapy of people with SARS-CoV-2 infection. Outcomes critical to this review are in bold.

- **All-cause mortality** at up to day 28, day 60, time-to-event, and at hospital discharge.
- **Clinical status**, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO

2020d) at up to day 28, day 60, and up to longest follow-up), including:
  * improvement of clinical status:
    - ☐ liberation from invasive mechanical ventilation in surviving participants;
    - ☐ ventilator-free days;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving participants;
    - ☐ duration to liberation from supplemental oxygen.
  * worsening of clinical status:
    - ☐ new need for mechanical ventilation (defined as high-flow oxygen, non-invasive, or invasive mechanical ventilation);
    - ☐ new need for invasive mechanical ventilation;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen;
    - ☐ new need for oxygen by mask or nasal prongs.
- Need for dialysis at up to day 28.
- **Quality of life**, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days, up to 30 days, and longest follow-up available.
- Need for admission to ICU.
- Duration of ICU length of stay, or time to discharge from ICU.
- Duration of hospitalisation, or time to discharge from hospital.
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days.
- **Serious adverse events**, defined as number of participants with event.
- **Adverse events** (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event.

Timing of outcome measurement

In the case of time-to-event analysis (e.g. for time to discharge from hospital and time to mortality), we included the outcome measure based on the longest follow-up time. We also collected information on outcomes from all other time points reported in the publications.

We included adverse events occurring during active treatment and as well as long-term adverse events. If sufficient data were available, we grouped the measurement time points of eligible outcomes, for example adverse events and serious adverse events, into those measured directly after treatment (up to 7 days after treatment), medium-term outcomes (up to 15 days after treatment), and longer-term outcomes (more than 30 days after treatment).

We combined three different types of advanced respiratory support (high-flow oxygen, non-invasive mechanical ventilation, and invasive mechanical ventilation) into one outcome measure, using the term 'mechanical ventilation' for clinical as well as patient-oriented reasons (see Differences between protocol and review).

Search methods for identification of studies

Electronic searches

Our Information Specialist (MIM) conducted systematic searches in the following sources from the inception of each database to 16 April 2021 (date of last search for all databases), placing no restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (https://covid-19.cochrane.org/) comprising:
  * Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates;
  * PubMed, daily updates;
  * Embase.com, weekly updates;
  * ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
  * World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/trialsearch), weekly updates;
  * medRxiv (www.medrxiv.org), weekly updates.
- Web of Science Clarivate:
  * Science Citation Index Expanded;
  * Emerging Sources Citation Index.
- WHO COVID-19 Global literature on coronavirus disease (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).

For detailed search strategies, see Appendix 1.

Searching other resources

We identified other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews, and meta-analyses. In addition, we contacted investigators of the included studies to obtain additional information on the retrieved studies.

We searched for grey literature, which we defined as searching study registries such as ClinicalTrials.gov and the WHO ICTRP, contained in the CCSR, as well as searching preprint servers and grey literature indexes contained in CCSR and WHO COVID-19 Global literature on coronavirus disease. Once we established our set of included studies, we searched for preprints via Europe PubMed Central, to check if any preprints for included studies had been published since our database search.

Data collection and analysis

Selection of studies

Four review authors (KA, FG, KD, VT) independently screened the results of the search strategies for eligibility by reading the titles and abstracts using Covidence software (Covidence 2021). We coded the abstracts as either 'include' or 'exclude'. In the case of disagreement, or if it was unclear whether the abstract should be retrieved, we obtained the full-text publication for further discussion. Several review authors (KA, FG, KD, VT) assessed the full-text articles of the selected studies. If two review authors were unable to reach a consensus, they consulted a third review author to reach a final decision.

As recommended in the PRISMA statement (Moher 2009), we documented the study selection process in a flow chart showing the total numbers of retrieved references and the numbers of included

and excluded studies. We listed all studies excluded after full-text assessment and the reasons for their exclusion in the Excluded studies section.

Data extraction and management

We conducted data extraction according to the guidelines proposed by Cochrane (Li 2020a). Several review authors (KA, FG, KD, VT, AM) extracted data independently and in duplicate, using a customised data extraction form developed in Microsoft Excel (Microsoft 2018). Any disagreements were resolved by discussion or by consulting a third review author if necessary.

Two out of several review authors (KA, FG, KD, AM, VT, VP) independently assessed the included studies for methodological quality and risk of bias. If the review authors were unable to reach a consensus, a third review author was consulted.

We extracted the following information, where reported.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Study characteristics: trial design, setting, and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up.
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, additional diagnoses, severity of disease, previous treatments, concurrent treatments, comorbidities (e.g. diabetes, respiratory disease, hypertension, immunosuppression, obesity, heart failure).
- Interventions: dosage, frequency, timing, duration and route of administration, setting, duration of follow-up.
- Control interventions (placebo or standard care alone): dosage, frequency, timing, duration and route of administration, setting, duration of follow-up.
- Outcomes: as specified in Types of outcome measures section.
- Risk of bias assessment: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result.

Assessment of risk of bias in included studies

We used the RoB 2 tool (beta version 7) to analyse the risk of bias of the included studies (Sterne 2019). Of interest in this review was the effect of the assignment to the intervention (the intention-to-treat effect), thus we performed all assessments with RoB 2 on this effect. The outcomes that we assessed are those specified for inclusion as described in the Methods section.

Two out of several review authors (KA, FG, KD, AM, VT, VP) independently assessed the risk of bias for each outcome using the RoB 2 Excel tool to manage and record assessments. In case of discrepancies amongst judgements and inability to reach consensus, a third review author was consulted reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021c).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For cluster-RCTs, we had planned to add a domain to assess bias arising from the timing of identification and recruitment of participants in relation to timing of randomisation, as recommended in the archived RoB 2 guidance for cluster-randomised trials and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Eldridge 2016; Higgins 2021b).

To address these types of bias, we used the signalling questions recommended in RoB 2 and made a judgement according to the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'Probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'Probably no': a judgement has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No information': if the study report does not provide sufficient information to permit a judgement.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

We subsequently derived an overall risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judge the trial to be at low risk of bias for all domains for the result.
- 'Some concerns': we judge the trial to raise some concerns in at least one domain for the result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result, or we judge the trial to have some concerns for multiple domains in a way that substantially lowers our confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (beta version 7, available from riskofbias.info), and stored and presented our detailed RoB 2 assessments in the analyses section and as supplementary online material.

For domain three of the tool ('bias due to missing outcome data'), we considered death as a competing risk factor, especially for dichotomous clinical progression outcomes. We judged improvement to be at high risk of bias due to missing data because it is likely that death during follow-up impeded liberation from respiratory support, and hence missing data on improvement depends on its true value.

Measures of treatment effect

For continuous outcomes, we recorded the mean, standard deviation, and total number of participants in both the treatment and control groups. Where continuous outcomes used the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we performed analyses using the standardised mean difference (SMD). In our interpretation of SMDs, we re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact (e.g. clinical symptoms with the WHO Clinical Progression Scale) (WHO 2020d).

For dichotomous outcomes, we recorded the number of events and the total number of participants in both the treatment and control groups. We reported the pooled risk ratio (RR) with its associated 95% CI, and risk difference (RD) with its associated 95% CI (Deeks 2020).

If sufficient information was available, we extracted and reported hazard ratios (HRs) for time-to-event outcomes (e.g. time to hospital discharge). If HRs were not available, we made every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney (Parmar 1998; Tierney 2007). If a sufficient number of studies provided HRs, we used HRs rather than RRs or MDs in a meta-analysis, as they provide more information.

Unit of analysis issues

The aim of this review was to summarise trials that analyse data at the level of the individual. We would also have accepted cluster-randomised trials for inclusion had any been identified. We collated multiple reports of a given study so that each study, rather than each report, was the unit of analysis.

Studies with multiple treatment groups

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021d), for studies with multiple treatment groups of the same intervention (i.e. dose, route of administration), we planned to evaluate if study arms were sufficiently homogeneous to be combined. We planned that if study arms could not be pooled, we would compare each arm with the common comparator separately. For pair-wise meta-analysis, we planned to split the 'shared' group into two or more groups with a smaller sample size, and include two or more (reasonably independent) comparisons. For this purpose, both the number of events and the total number of participants would have been divided for dichotomous outcomes, and the total number of participants would have been divided with unchanged means and standard deviations for continuous outcomes.

One study included in the review had multiple treatment arms of the same intervention (5-day course of remdesivir versus 10-day course of remdesivir) (Spinner 2020). Given the small number of participants in this study, we did not perform meta-analysis, but have reported the results for each treatment arm narratively in our subgroup analysis (see Effects of interventions, Duration of remdesivir application).

Dealing with missing data

In Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions*, a number of potential sources for missing data are suggested, which we took into account: at study level, at outcome level, and at summary data level (Deeks 2020). At all levels, it is important to differentiate between data 'missing at random', which may often be unbiased, and 'not missing at random', which may bias the study and in turn the review results.

In the case of missing data, we requested this information from the principal investigators; details are provided in the Included studies section. Beigel 2020 and Spinner 2020 provided additional data on all-cause mortality at up to day 28 for subgroups of respiratory support, and Spinner 2020 provided data on clinical course. If after this data were still missing, we had to make explicit assumptions of any methods the included studies used.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level of $P < 0.1$. We used the I^2 statistic, Higgins 2003, and visual examination of the forest plot, to assess possible heterogeneity ($I^2 > 30\%$ to signify moderate heterogeneity, $I^2 > 75\%$ to signify considerable heterogeneity) (Deeks 2020). We planned that if the I^2 was above 80%, we would explore possible causes of heterogeneity through sensitivity analyses. If we could not find a reason for heterogeneity, we would not perform a meta-analysis, but instead would comment on the results from all studies and present these in tables.

Assessment of reporting biases

As mentioned above, we searched the trials registries to identify completed trials that have not been published elsewhere, to minimise publication bias or determine publication bias. We intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials (Sterne 2019). We would consider $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analysis. We performed analyses according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). We planned to treat placebo and no treatment as the same intervention, as well as standard care at different institutions and time points.

We used the Review Manager Web (RevMan Web) software for analyses (RevMan Web 2021). One review author entered the data into the software, and a second review author checked the data for accuracy. We used the random-effects model for all analyses, as we anticipated that true effects would be related but not the same for included studies. We planned that if meta-analysis was not possible, we would comment on the results narratively with the results from all studies, and present these in tables. If meta-analysis was possible, we would assess the effects of potential biases in sensitivity analyses (see Sensitivity analysis). For binary outcomes, we based the estimation of the between-study variance using the Mantel-Haenszel method. We used the inverse-variance method for continuous outcomes, outcomes that included data from cluster-RCTs, or outcomes where HRs were available. We explored heterogeneity for the outcome clinical worsening: new need for mechanical ventilation ($I^2 = 85\%$)

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses for all-cause mortality at up to day 28 exclusively. In the case of sufficient data, we performed subgroup analyses of the following characteristics for remdesivir versus placebo or standard care alone.

- Age of participants (divided into applicable age groups, e.g. 18 to 65 years, 65 to 79 years, 80 years and older).
- Pre-existing conditions (e.g. diabetes, respiratory disease, hypertension, immunosuppression, obesity, cardiac injury).
- Timing of first dose administration with illness onset.
- Severity of condition:
  * no oxygen versus low-flow oxygen versus mechanical ventilation (including high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation).
- Duration of remdesivir application:
  * 5-day course of remdesivir versus 10-day course of remdesivir.

We used the tests for interaction to test for differences between subgroup results.

Sensitivity analysis

We performed sensitivity analysis of the following study characteristics for our prioritised outcomes, as described in the Types of outcome measures section.

- Risk of bias assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias).
- Comparison of preprints versus peer-reviewed articles.
- Comparison of premature termination of studies with completed studies.
- Comparison of adolescent and adult participants versus adult participants.

Summary of findings and assessment of the certainty of the evidence

We created Summary of findings 1 and evaluated the certainty of the evidence using the GRADE approach for interventions evaluated in RCTs.

Summary of findings

We used MAGICapp software to create summary of findings tables (MAGICapp). For time-to-event outcomes, we calculated absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020).

Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions* specifies that the "most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes" should be included in the summary of findings table(s) (Schünemann 2021). We included outcomes prioritised according to the Core Outcome Set for intervention studies, COMET 2020, and patient relevance; these are listed below.

- **All-cause mortality**: all-cause mortality at hospital discharge most favourable; if not reported, we will include all-cause mortality day 60, followed by day 28, or time-to-event estimate in the summary of findings table.
- **Improvement of clinical status**, assessed with liberation from supplemental oxygen support or invasive mechanical ventilation, in accordance with WHO Clinical Progression Scale (WHO 2020d), at longest follow-up available.
  * For all hospitalised individuals with oxygen support (WHO ≥ 5 at baseline on the WHO Clinical Progression Scale) (WHO 2020d): liberation from supplemental oxygen in surviving participants most favourable; if not reported, we will include duration to liberation from supplemental oxygen in the summary of findings table.
  * For the subgroup of severely ill individuals (WHO ≥ 7 at baseline on the WHO Clinical Progression Scale) (WHO 2020d): liberation from invasive mechanical ventilation in surviving participants most favourable; if not reported, we will include ventilator-free days, followed by duration to liberation from invasive mechanical ventilation, in the summary of findings table.
- **Worsening of clinical status**, assessed with new need for respiratory support, in accordance with the WHO Clinical Progression Scale (WHO 2020d), at longest follow-up available.
  * New need for mechanical ventilation (non-invasive ventilation or high-flow oxygen or invasive ventilation).
  * New need for invasive mechanical ventilation.
  * New need for non-invasive mechanical ventilation or high-flow oxygen.
  * New need for oxygen by mask or nasal prongs.
- **Quality of life**, including fatigue and functional independence, assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available.
- **Adverse events** (any grade).
- **Serious adverse events.**

Assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the outcomes listed above.

The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each prioritised outcome.

We downgraded the certainty of the evidence for:

- serious (−1) or very serious (−2) risk of bias;
- serious (−1) or very serious (−2) inconsistency;
- serious (−1) or very serious (−2) uncertainty about directness;
- serious (−1) or very serious (−2) imprecise or sparse data;
- serious (−1) or very serious (−2) probability of reporting bias.

The GRADE system uses the following criteria for assigning grades of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021).

We used the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading the certainty of the evidence for risk of bias. We phrased the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020).

Methods for future updates

Living systematic review considerations

Our Information Specialist (MIM) will provide us with new search records each week, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Cochrane LSR). We will manually check platform trials that were previously identified and listed as 'studies awaiting classification' for additional treatment arms. We will wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We will consider one or more of the following components to inform this decision.

- Findings that change the estimated effect of one or more prioritised outcomes.
- Findings that change the credibility (e.g. GRADE rating) of the estimated effect of one or more prioritised outcomes.
- New settings, populations, interventions, comparisons, or outcomes studied.

In case of emerging policy relevance because of global controversies around the intervention, we will consider republishing an updated review even though our conclusions remain unchanged. We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (e.g. when additional comparisons, interventions, subgroups or outcomes, or new review methods become available).

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

We performed the database searches for RCTs in April 2021 and identified 922 records. After removing duplicates, we screened 884 records based on title and abstract, of which 783 studies did not meet the prespecified inclusion criteria and were excluded. We screened the full texts, or if these were not available, the trial register entries, of the remaining 101 references. Reasons for exclusion of the studies excluded at full-text stage are listed in Characteristics of excluded studies. We identified two ongoing records (two studies) (Characteristics of ongoing studies; Table 2). Overall, we included 42 records (five studies) in our narrative analysis and 41 records (four studies) in our meta-analyses. We searched ClinicalTrials.gov and the WHO ICTRP for additional and ongoing trials that met our inclusion criteria. Details of our search strategy are provided in Appendix 1. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1).

Figure 1.

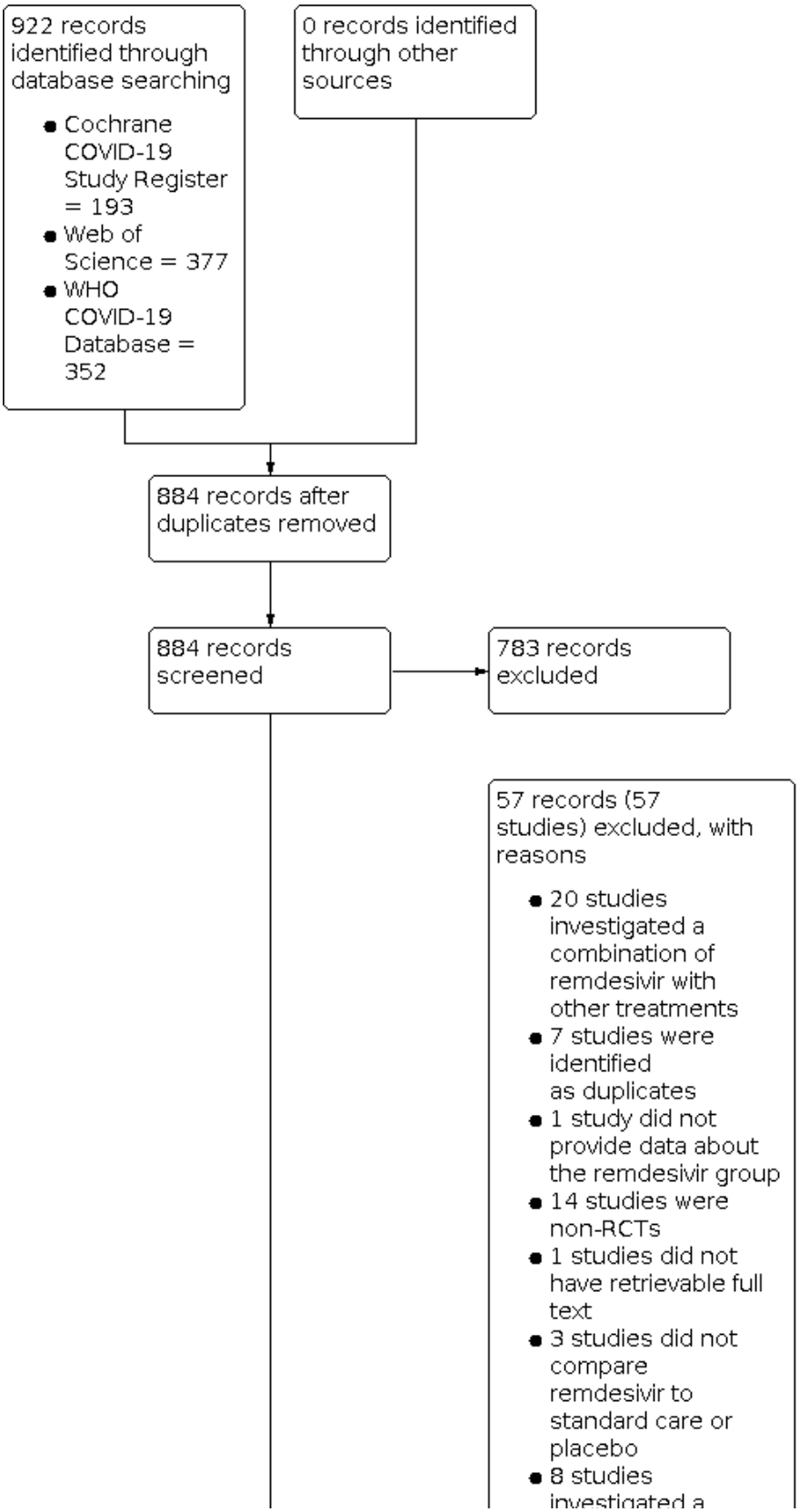
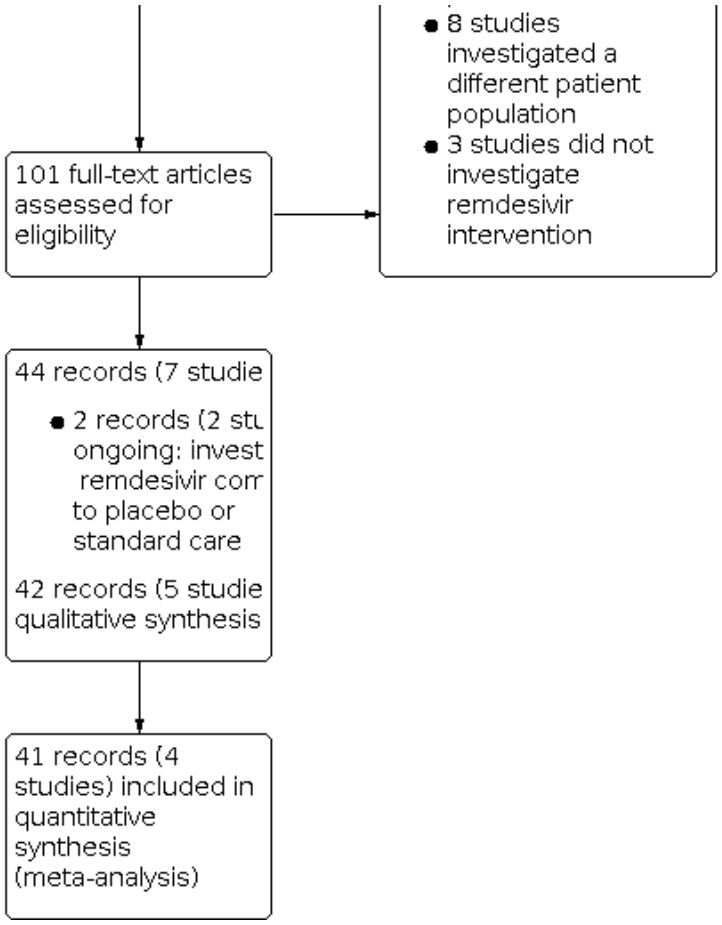


Figure 1. (Continued)



Included studies

We included five RCTs with 7452 participants diagnosed with SARS-CoV-2 infection in the review (Beigel 2020; Spinner 2020; Wang 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021). The included participants (mean age 59.37 years, 63.31% male) were diagnosed with SARS-CoV-2 infection and were randomly assigned to receive either remdesivir or standard care alone. The majority of included studies were conducted in high- and upper-middle-income countries; the only reported lower-middle-income countries were Honduras, India, and the Philippines. A detailed overview of the characteristics of included studies is provided in Characteristics of included studies and Table 3.

Study design and control

All included RCTs used a parallel-group design. Three studies had an open-label design with comparison of remdesivir to standard care alone (Spinner 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021), whereas two studies were double-blinded and placebo-controlled (Beigel 2020; Wang 2020). In one study (Beigel 2020), participants in the control arm received a lyophilised placebo identical in physical appearance to the active lyophilised formulation and containing the same inactive ingredients; alternatively, a normal saline of equal volume was given if there were limitations on matching placebo supplies. In the other study (Wang 2020), participants in the control group received a placebo, which was provided by Gilead Sciences. Three studies compared remdesivir to standard care alone (Spinner 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021). Notably, two studies did not provide details on standard care (Wang 2020; Mahajan 2021). Three studies performed non-specified standard care according to local guidelines (Beigel 2020; Spinner 2020; WHO Solidarity Trial Consortium 2021).

Intervention

A total of 3886 participants in the included RCTs were randomised to receive remdesivir. The majority of included studies applied a 10-day course of remdesivir (Beigel 2020; Spinner 2020; Wang 2020; WHO Solidarity Trial Consortium 2021). Spinner 2020 (additionally) and Mahajan 2021 (solely) reported outcomes also for a five-day treatment course. Participants in the WHO Solidarity trial were randomly assigned to receive either remdesivir (n = 2750), hydroxychloroquine (n = 954), lopinavir (n = 1411), or interferon beta-1a (n = 2063) and were compared with a control group for each arm (WHO Solidarity Trial Consortium 2021). Because of an overlap of each control group with other groups, participants allocated for experimental treatments other than remdesivir and associated control groups were not included in the total calculation of participants in our review.

The treatment regimen in the interventional arms of all included studies consisted of standard care plus 200 mg remdesivir intravenously as a loading dose on day 1, followed by 100 mg daily. In three studies (Beigel 2020; Wang 2020;

WHO Solidarity Trial Consortium 2021), the maintenance dose plus standard care was administered on days 2 through 10 or until hospital discharge or death. In one study (Spinner 2020), participants received maintenance dose plus standard care either for four or nine consecutive days or until hospital discharge or death; and in the remaining study (Mahajan 2021), the maintenance dose of 100 mg remdesivir plus standard care was administered daily on days 2 through 5.

Setting

Three studies were multicentre studies performed in several countries (Beigel 2020 in 73 sites in Denmark, Germany, Greece, Japan, Korea, Mexico, Singapore, Spain, the UK, and the USA; Spinner 2020 in 105 hospitals in Asia, Europe, and the USA; WHO Solidarity Trial Consortium 2021 in 405 hospitals in Argentina, Brazil, Canada, Germany, Honduras, India, Indonesia, Iran, Ireland, Israel, Italy, Kenya, Lebanon, Malaysia, Norway, Peru, the Philippines, Qatar, Saudi Arabia, South Africa, Spain, Switzerland, and Thailand) (Beigel 2020; Spinner 2020; WHO Solidarity Trial Consortium 2021). Wang 2020 performed a multicentre study in one country, China. Mahajan 2021 performed a single-centre study in India.

Participants

All studies included hospitalised adults with SARS-CoV-2 infections (Beigel 2020; Spinner 2020; Wang 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021). Notably, Spinner 2020 included one participant younger than 18 years; this corresponds to 0.178% of all recruited participants in this RCT. Reported comorbidities across all studies included diabetes, hypertension and other cardiovascular diseases, chronic lung disease or liver disease, and obesity. Full details on comorbidities are provided in Table 3.

Diagnosis of SARS-CoV-2 infection

In four studies (Beigel 2020; Spinner 2020; Wang 2020; Mahajan 2021), SARS-CoV-2 infection diagnosis was confirmed by PCR and clinical or radiological signs of pneumonia. In two studies (Spinner 2020; WHO Solidarity Trial Consortium 2021), participants were included with "definite" SARS-CoV-2 infection without further specification, or rather with clinical signs of an acute respiratory infection. The included studies did not provide details on how many participants' SARS-CoV-2 infection was confirmed by PCR testing.

Severity of illness

No two studies reported similar subgroups of participants in terms of severity of illness. Three studies included participants with moderate to severe illness, although according to different definitions (Beigel 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021, Table 4). One study included participants with moderate illness (Spinner 2020); and one study included participants with severe illness (Wang 2020). In Beigel 2020, participants were considered to have severe disease if they required mechanical ventilation; if the oxygen saturation as measured by pulse oximetry (SpO_2) was 94% or lower whilst they were breathing ambient air; or if they had tachypnoea (respiratory rate ≥ 24 breaths per minute). The majority of participants in this study met the aforementioned criteria and needed supplemental oxygen (intervention 42.9%, control 39.0%), non-invasive ventilation or high-flow oxygen (intervention 17.6%, control 18.8%), or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (intervention 24.2%, control 29.6%). Only 13.9% of participants in the intervention arm and 12.1% of participants in the control arm were hospitalised without requiring supplemental oxygen. In Mahajan 2021, participants in both groups were classified as "highest disease severity", but were excluded from the study if receiving mechanical ventilation or if having multi-organ failure. The majority (79.4%) of participants in the intervention group versus 72.2% of participants in the control group received low-flow supplemental oxygen, and 20.6% versus 27.8% received non-invasive ventilation or high-flow oxygen, respectively. In Spinner 2020, the majority (84%) of participants in the intervention group versus 80% of participants in the control group did not require supplemental oxygen. Although measured oxygen saturation at screening was above 94% whilst breathing room air, 13% of participants in the intervention group and 19% in the control group used supplemental oxygen because of deteriorating clinical status or for breathing comfort. In Wang 2020, severe SARS-CoV-2 infections was defined by 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. The majority of participants in this study needed oxygen supplementation (intervention 82%, control 83%), whilst non-invasive ventilation or high-flow oxygen was necessary in 18% and 12% of participants, respectively. Invasive mechanical ventilation or ECMO was only required in 1% of the control group and none in the intervention group. In WHO Solidarity Trial Consortium 2021, disease severity was not protocol-defined, but baseline respiratory support was divided in "no supplemental oxygen", "supplemental oxygen", and "mechanical ventilation". The majority of participants in the intervention group (66.6%) and the control group (66.9%) received supplemental oxygen at entry, whilst no supplemental oxygen was needed in 24.1% and 24.5% of participants in each group. The minority of participants received mechanical ventilation at entry: 9.3% and 8.6%, respectively.

Concomitant medications

Concomitant use of COVID-19 medication was restricted to heparin and corticosteroids in one study (Mahajan 2021). Wang 2020 reported concomitant use of lopinavir–ritonavir, interferon, and corticosteroids. Two studies provided no details on concomitant therapy (Beigel 2020; WHO Solidarity Trial Consortium 2021). Additional therapy with traditional herbs including sho-saiko-to (or Xiao-Shai-Hu-Tang) or investigational agents with putative antiviral activity against COVID-19 was prohibited by protocol for participants receiving remdesivir in one study (Spinner 2020). However, concomitant use of lopinavir-ritonavir, hydroxychloroquine/chloroquine, interferon, steroids, tocilizumab, and azithromycin was reported for all participants, predominantly in the control arm.

Outcomes

Primary outcomes differed significantly between included studies, with no two studies having chosen the same primary endpoint (Beigel 2020: time to recovery; Mahajan 2021: improvement in clinical outcomes; WHO Solidarity Trial Consortium 2021: all-cause mortality; Spinner 2020: clinical status on day 11; Wang 2020: time to clinical improvement at day 28). A detailed narrative summary of all reported outcome measures for each of the included studies is provided in Table 5.

Ongoing studies

An overview of the characteristics of ongoing studies is provided in Characteristics of ongoing studies and Table 2. We included two records of ongoing studies comparing the effects of remdesivir with placebo or standard care alone (NCT04252664; NCT04596839). NCT04596839 was expected to be completed in 2021 and planned to evaluate 60 participants. NCT04252664 was discontinued: "The epidemic of COVID-19 has been controlled well at present, no eligible patients can be recruited". They had planned to evaluate 308 participants.

Excluded studies

We excluded 57 references (57 studies) that did not match our inclusion criteria (for details, see Characteristics of excluded studies):

- Seven references were identified as duplicates;
- For one reference the full-text was not retrievable;
- 14 studies were non-RCTs;
- 20 studies investigated a combination of remdesivir with other treatments;
- Three studies did not compare remdesivir to standard care or placebo;
- Eight studies investigated a different patient population;
- One study did not provide data on the remdesivir group;
- Three studies did not investigate remdesivir intervention.

Risk of bias in included studies

We assessed risk of bias for the results within the five included RCTs, Beigel 2020; Spinner 2020; Wang 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021, using the RoB 2 tool, as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2019; Higgins 2021c). Outlined below are outcomes that were reported according to our review protocol. The completed RoB 2 tool with responses to all assessed signalling questions is available online at https://doi.org/10.5281/zenodo.5101320.

Remdesivir compared to placebo or standard care alone

All-cause mortality

Four studies reported this outcome (see Risk of bias table for Analysis 1.1). Overall, we rated the risk of bias for mortality to be low for three studies (Beigel 2020; Spinner 2020; WHO Solidarity Trial Consortium 2021), and of some concerns for one study (Wang 2020). We assessed this outcome on a study level at up to day 28 and as time-to-event or at hospital discharge, if provided (see Risk of bias table for Analysis 1.2; Risk of bias table for Analysis 1.3), as well as for our subgroup analyses (see Risk of bias table for Analysis 2.1; Risk of bias table for Analysis 3.1; Risk of bias table for Analysis 4.1). For one study (Wang 2020), there were some concerns arising from baseline differences in gender distribution, respiratory status, comorbidities, and time from symptom onset, suggesting a possible problem with block wise and stratified randomisation process. We did not identify any concerns that could have biased the reported outcome in three studies (Beigel 2020; Spinner 2020; WHO Solidarity Trial Consortium 2021), and therefore judged the risk of bias to be low.

Clinical status

Three studies reported this outcome (see Risk of bias table for Analysis 1.4; Risk of bias table for Analysis 1.5; Risk of bias table for Analysis 1.6; Risk of bias table for Analysis 1.7). We assessed this outcome on a study level by the need for respiratory support in accordance with a standardised scale (WHO 2020d), and included both clinical improvement and worsening in our assessment. Liberation of supplemental oxygen or invasive mechanical ventilation was reported in one study at day 15 (Beigel 2020), and therefore not included in our analyses. Duration to liberation from supplemental oxygen or invasive mechanical ventilation was reported by two and three studies, respectively (Beigel 2020; Spinner 2020; Wang 2020), but data could not be pooled and are therefore described narratively. Two studies provided data on clinical worsening (Beigel 2020; WHO Solidarity Trial Consortium 2021). Although detailed information on randomisation process was not provided in Beigel 2020, blinding was appropriate, and outcome measurement and analyses were according to a prespecified protocol. However, due to competing risk of death, we judged some concerns for risk of bias due to missing data (RoB 2, domain 3) for dichotomous worsening outcomes, and high risk of bias for dichotomous improvement outcomes. We assessed improvement as at high risk of bias due to missing data because it is likely that death during follow-up impeded liberation from respiratory support, and hence the missing data on improvement depends on its true value. Spinner 2020 provided additional data on need for invasive mechanical ventilation after author enquiry. Given a relevant deviation of assessment time point, an open-label study design, and a competing risk of death, we judged the outcome measurement as at high risk of bias.

Duration of hospitalisation

Three studies reported this outcome (see RoB 2.0 Tool assessment). We assessed this outcome on a study level for length of hospital stay in days. Since Beigel 2020 and Wang 2020 reported data as median, and WHO Solidarity Trial Consortium 2021 and Spinner 2020 only provided figures for this outcome, meta-analysis could not be conducted. Together with the reporting of Mahajan 2021, we have presented data on this outcome narratively (see Table 5). Risk of bias has still been assessed where possible and was judged to be low for Beigel 2020. Some concerns arose with baseline differences in Wang 2020. Given an inexplicit randomisation process and concealment, a deviation from intended intervention, a relevant amount of missing data, and an inappropriate outcome measurement and analysis, we judged Mahajan 2021 as at high risk of bias.

Viral clearance

One study reported this outcome (see Risk of bias table for Analysis 1.8). We assessed this outcome on a study level with RT-PCR test for SARS-CoV-2 at baseline and up to three, seven, 15, and 28 days. Only Wang 2020 provided data for this outcome and was judged as at high risk of bias due to baseline differences, a relevant amount of missing outcome data, and selective reporting.

We could not conduct risk of bias assessment for quality of life, need for dialysis, need for admission to ICU, duration of ICU length of stay, or time to discharge from ICU as none of these outcomes were reported.

Serious adverse events

Three studies reported this outcome (see Risk of bias table for Analysis 1.9) and were judged with some concerns (Beigel 2020; Spinner 2020; Wang 2020). This judgement in Beigel 2020 was based on inappropriate analyses and selection of participants, which did not comply with the appropriate safety population. We assessed Wang 2020 as some concerns due to baseline differences between the intervention and control group. For Spinner 2020, there was a low risk arising from the awareness of the assigned intervention (open-label), which is unlikely to have affected the outcome measurement. However, we judged missing outcome data as some concerns of bias in all studies due to competing risk of death without evidence, that missing outcome data does not depend on its true value.

Adverse events (any grade)

Three studies reported these outcomes (see Risk of bias table for Analysis 1.10; Risk of bias table for Analysis 1.11). We identified some concerns for risk of bias in Beigel 2020 and Wang 2020 due to inappropriate analysis (as-treated population) and differences in baseline characteristics, respectively. Some concerns also arose from the open-label study design in Spinner 2020, particularly in the reporting of lower-grade adverse events in participants who were aware of the intervention. Additionally, adverse events grade three and higher were not compared between groups as stated by the statistical analysis plan. We judged missing outcome data as some concerns in all studies due to competing risk of death without evidence, that missing outcome data does not depend on its true value.

Effects of interventions

See: **Summary of findings 1** Remdesivir compared to placebo or standard care alone for hospitalised adults with confirmed SARS-CoV-2 infection

See: Summary of findings 1 Remdesivir compared to placebo or standard care alone for adult in-hospital participants with confirmed SARS-CoV-2 infection.

Remdesivir compared to placebo or standard care alone

We have presented the summary of findings and the certainty of the evidence for adult in-hospital participants with confirmed SARS-CoV-2 infection, comparing a 10-day course of remdesivir to placebo or standard care alone.

All-cause mortality

We assessed all-cause mortality at up to day 28, as time-to-event and at hospital discharge. We did not find data for all-cause mortality beyond day 28.

All-cause mortality at up to day 28

Four studies reported this outcome for 7142 participants (see Analysis 1.1). Considering the reported event rates across studies, we found that remdesivir probably makes little or no difference to all-cause mortality at up to day 28 compared to placebo or standard care (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.81 to 1.06; risk difference (RD) 8 fewer per 1000, 95% CI 21 fewer to 7 more; 4 studies, 7142 participants; I^2 = 0%; moderate-certainty evidence). Our main reasons for downgrading were serious imprecision because of wide confidence intervals in the studies, and the 95% confidence interval includes both benefits and harms.

All-cause mortality at hospital discharge

One study reported this outcome for 5451 participants (see Analysis 1.2). The outcome occurred in 301 of 2743 cases in the remdesivir group and 303 of 2708 cases in the control group. Treatment with remdesivir resulted in no difference in all-cause mortality at hospital discharge (RR 0.98, 95% CI 0.84 to 1.14; 1 study, 5451 participants; I^2 not applicable).

All-cause mortality, time to event

Two studies reported this outcome for 6513 participants (see Analysis 1.3). Treatment with remdesivir resulted in no difference in mortality when measured over time (hazard ratio (HR) 0.93, 95% CI 0.80 to 1.07; 2 studies, 6513 participants; I^2 = 57%). One study reported median number of days for 236 participants and was described narratively (Wang 2020). The median (interquartile (IQR)) number of days from randomisation to death for 158 participants in the remdesivir group and 78 participants in the control group was 9.5 days (IQR 6.0 to 18.5) and 11.0 days (IQR 7.0 to 18.0), respectively. A Kaplan-Meier curve was not provided, and a hazard ratio could not be estimated.

Improvement of clinical status

For clinical improvement, the included studies reported various parameters with differing scales (see Table 5).

Liberation from invasive mechanical ventilation in surviving participants

Reporting of clinical status was not provided according to our outcome definition. Only one study reported this outcome (Beigel 2020), at day 15 for 1062 participants; for details, see Table 5.

Ventilator-free days

We did not find any data for this outcome.

Duration to liberation from invasive mechanical ventilation

Two studies reported this outcome in median days, which did not allow meta-analysis, and is therefore presented narratively. Beigel 2020 reported a median of 17 days (IQR 9 to 28) to liberation from invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) after receiving remdesivir, compared to 20 days (IQR 8 to 28) in the control group (rate difference −3.0, 95% CI −9.3 to 3.3; 1062 participants). In Wang 2020, participants stayed on invasive mechanical ventilation or ECMO for a median of 7 days (IQR 4 to 16) in the remdesivir group versus 15.5 days (IQR 6 to 21) in the control group (rate difference −4.0, 95% CI −14.0 to 2.0; 236 participants). Remdesivir may have little or no effect on clinical improvement defined as duration to liberation from invasive mechanical ventilation at up to day 28 (2 studies, 1298 participants; low-certainty evidence). Our main reasons for downgrading were serious risk of bias because of competing risk of death, and serious imprecision because the 95% confidence interval includes both benefits and harms.

Liberation from supplemental oxygen in surviving participants

Reporting of clinical status was not provided according to our outcome definition. Only one study reported this outcome (Beigel 2020), at day 15 for 1062 participants; for details, see Table 5.

Duration to liberation from supplemental oxygen up to day 28

Three studies reported this outcome in median days, which did not allow for meta-analysis, and is therefore presented narratively. Beigel 2020 reported a median of 13 days (IQR 5 to 28) until liberation from supplemental oxygen after receiving remdesivir, compared to a median of 21 days (IQR 8 to 28) in the control group (rate difference −8.0, 95% CI −11.8 to −4.2; 1062 participants). In Wang 2020, participants stayed on supplemental oxygen for a median of 19 days (IQR 11 to 30) in the remdesivir group, compared to 21 days (IQR 14 to 30.5) in the control group (rate difference −2, 95% CI −6.0 to 1.0; 236 participants). Contrary to the aforementioned studies, Spinner 2020 provided time to room air regardless of the initial respiratory support. Participants in the 10-day remdesivir arm needed a median of 4 days (IQR 2 to 6) of supplemental oxygen compared to a median of 6 days (IQR 4 to 14) in the control group (HR 1.93, 95% CI 1.11 to 3.36; 393 participants). We are uncertain whether remdesivir increases or decreases the chance of clinical improvement defined as duration to liberation from supplemental oxygen at up to day 28 (3 studies, 1691 participants; very low-certainty evidence). Our main reasons for downgrading were serious risk of bias because of inadequate blinding of participants, personnel, and outcome assessors, and possible deviation in time point of measuring in one study, and because of competing risk of death. Further reasons for downgrading were serious imprecision because the 95% confidence interval includes both benefits and harms, and studies reported outcomes differently because of missing standards.

Worsening of clinical status

New need for mechanical ventilation up to day 28 (defined as high-flow oxygen or non-invasive ventilation or invasive mechanical ventilation)

Three studies reported new need for mechanical ventilation for 6696 participants, if not received at baseline (see Analysis 1.4). Considering the reported event rates across studies, the evidence is very uncertain regarding the effects of remdesivir on the risk of clinical worsening: new need for mechanical ventilation within 28 days when compared to placebo or standard care (RR 0.78, 95% CI 0.48 to 1.24; RD 29 fewer per 1000, 95% CI 68 fewer to 32 more; 3 studies, 6696 participants; I^2 = 85%; very low-certainty evidence). Our main reasons for downgrading were serious imprecision because of wide confidence interval in the studies; serious inconsistency because of statistical heterogeneity; and serious risk of bias. Reasons for risk of bias were inadequate blinding of participants, personnel, and outcome assessors, as well as possible deviation in time point of measuring in one study and competing risk of death.

New need for invasive mechanical ventilation up to day 28

Two of the three aforementioned studies reported new need for invasive mechanical ventilation for 1159 participants, if not received at baseline (see Analysis 1.5). Considering the reported event rates across studies, we found that remdesivir may decrease the risk of clinical worsening: new need for invasive mechanical ventilation within 28 days when compared to placebo or standard care (RR 0.56, 95% CI 0.41 to 0.77; RD 67 fewer per 1000, 95% CI 90 fewer to 35 fewer; 2 studies, 1159 participants; I^2 = 0%; low-certainty evidence). Our main reasons for downgrading were serious risk of bias because of inadequate blinding of participants, personnel, and outcome assessors, as well as possible deviation in time point of measuring in one study, and competing risk of death. Furthermore, studies reported outcomes differently because of missing standards.

New need for non-invasive mechanical ventilation or high-flow oxygen up to day 28

One study reported new need for non-invasive mechanical ventilation for 573 participants, if not received at baseline (see Analysis 1.6). Considering the reported event rates across studies, the evidence is very uncertain regarding the effects of remdesivir on the risk of clinical worsening: new need for non-invasive mechanical ventilation or high-flow oxygen within 28 days when compared to placebo or standard care (RR 0.70, 95% CI 0.51 to 0.98; RD 72 fewer per 1000, 95% CI 118 fewer to 5 fewer; 1 study, 573 participants; I^2 not applicable; very low-certainty evidence). Our main reasons for downgrading were serious risk of bias because of competing risk of death, and serious imprecision due to few participants and data from only one study.

New need for oxygen by mask or nasal prongs (low-flow oxygen) up to day 28

One study reported new need for oxygen by mask or nasal prongs for 138 participants, if not received at baseline (see Analysis 1.7). Considering the reported event rates across studies, the evidence is very uncertain regarding the effects of remdesivir on the risk of clinical worsening: new need for oxygen by mask or nasal prongs within 28 days when compared to placebo or standard care (RR 0.81, 95% CI 0.54 to 1.22; RD 84 fewer per 1000, 95% CI 204 fewer to 98 more; 1 study, 138 participants; I^2 not applicable; very low-certainty evidence). Our main reasons for downgrading were serious imprecision because of wide confidence intervals, and data coming from only one study.

Need for dialysis at up to day 28

We did not find any data for this outcome.

Quality of life

We did not find any data for this outcome.

Need for admission to ICU

We did not find any data for this outcome.

Duration of ICU length of stay or time to discharge from ICU

We did not find any data for this outcome.

Duration of hospitalisation or time to discharge from hospital

Five studies reported this outcome (see Table 5). Beigel 2020 reported median (IQR) days for 1062 participants. Participants receiving remdesivir treatment were hospitalised for a median of 12 days (IQR 6 to 28) compared to a median of 17 days (18 to 28) in the control group (rate difference −5, 95% CI −7.7 to −2.3). Wang 2020 reported the outcome for 236 participants, with a median duration of hospitalisation of 25 days (IQR 16 to 38) in the remdesivir group versus a median of 24 days (18 to 36) in the control group (rate difference 0, 95% CI −4.0 to 4.0). Additionally, Wang 2020 provided a median time to hospital discharge of 21 days in both groups (remdesivir 21.0 (IQR 12 to 31), control 21.0 (IQR 13.5 to 28.5); rate difference 0, 95% CI −3.0 to 3.0). Mahajan 2021 reported mean (standard deviation) of a five-day remdesivir course (remdesivir 11.55 (4.3) versus control 12.38 (5.2)).

Viral clearance

One study reported this outcome for 236 participants who tested positive at enrolment (see Analysis 1.8). Wang 2020 provided data on viral clearance (undetectable viral RNA from naso-/oropharyngeal swab) at baseline and at several time points, of which day 3, 7, and 15 were included as predefined in this review. In Wang 2020, viral clearance at day 14 was reported, which we used in our analysis. The study also visualised viral RNA load over time from baseline by quantitative PCR on the upper respiratory tract and lower respiratory tract and by duration of illness (≤ 10 days versus > 10 days). Undetectable viral RNA in upper respiratory tract was reported for 131 participants in the remdesivir group and 65 participants in the placebo group; 40 data sets were missing. Nasopharyngeal PCR for remdesivir versus placebo was negative in 24 versus 13 (RR 0.92, 95% CI 0.50 to 1.68) at baseline; 37 versus 19 (RR 0.97, 95% CI 0.61 to 1.54) at day 3; 66 versus 32 (RR 1.02, 95% CI 0.76 to 1.38) at day 7; and 93 versus 49 (RR 0.94, 95% CI 0.79 to 1.12) at day 14.

Overall, viral clearance in the positive population of the remdesivir and placebo arms increased over time, with 71% and 75.4% undetectable RNA at day 14, respectively. There was no significant difference between groups at any time point.

Serious adverse events

Three studies reported this outcome for 1674 participants (see Analysis 1.9). Considering the reported event rates across studies, we found that remdesivir probably decreases the risk of serious adverse events within 28 days when compared to placebo or standard care (RR 0.75, 95% CI 0.63 to 0.90; RD 63 fewer per 1000, 95% CI 94 fewer to 25 fewer; 3 studies, 1674 participants; I^2 = 0%; moderate-certainty evidence). We downgraded the certainty of evidence due to serious risk of bias because of competing risk of death.

Adverse events

Adverse events, any grade

Three studies reported this outcome for 1674 participants (see Analysis 1.10). Considering the reported event rates across studies, the evidence is very uncertain regarding the effects of remdesivir on adverse events (any grade) within 28 days when compared to placebo or standard care (RR 1.05, 95% CI 0.86 to 1.27; RD 29 more per 1000, 95% CI 82 fewer to 158 more; 3 studies, 1674 participants; I^2 = 77%; very low-certainty evidence). Our main reasons for downgrading were serious imprecision because of wide confidence intervals in the studies. We also downgraded for serious risk of bias because of competing risk of death, and serious inconsistency due to statistical heterogeneity.

Adverse events, grade 3 to 4

Three studies reported this outcome for 1674 participants (see Analysis 1.11). Considering the reported event rates across studies, we estimated that remdesivir results in 42 fewer participants sustaining at least one adverse event grade 3 to 4 compared to placebo or standard care alone amongst 1000 participants. Treatment with remdesivir probably results in little or no difference on the occurrence of adverse events grade 3 to 4 within 28 days when compared to placebo or standard care (RR 0.90, 95% CI 0.80 to 1.00; 3 studies, 1674 participants; I^2 = 0%; moderate-certainty evidence). Our main reasons for downgrading were serious risk of bias because of inadequate blinding of participants, personnel, and outcome assessors; one study stopped earlier than scheduled, and one study used an inappropriate patient population.

Subgroup analyses

We conducted subgroup analyses for prioritised effectiveness outcomes to explore heterogeneity between predefined subgroups. Since data were only available for mortality at up to day 28, analyses were performed exclusively for this outcome.

Age of participants

One study reported all-cause mortality at up to day 28 divided by age groups (< 50 years, 50 to 69 years, > 69 years) for 5451 participants (see Analysis 2.1). There were no subgroup differences (Chi^2= 0.10, df = 2, P = 0.95, I^2 not applicable).

Pre-existing conditions

Protocol-specified comorbidities included diabetes, respiratory disease, hypertension, immunosuppression, obesity, and cardiac injury. One study reported all-cause mortality at up to day 28 subdivided by pre-existing conditions of interest (WHO Solidarity Trial Consortium 2021). They compared the effect of remdesivir in one specific subgroup (e.g. with asthma) to a control without that condition (e.g. without asthma). However, since there is a partial overlap of comorbidities between subgroups, control groups might therefore involve participants with other pre-existing conditions of interest. As a result, meta-analysis not be conducted, and all-cause mortality at up to day 28 is reported narratively (see Table 5).

Timing of first dose administration with illness onset

One study reported all-cause mortality at up to day 28 divided by timing of first dose administration with illness onset for 233 participants (see Analysis 3.1). The evidence suggests a benefit for early initiation of treatment with remdesivir (≤ 10 days after symptom onset) compared to placebo or standard care alone (RR 0.76, 95% CI 0.29 to 1.95), whilst in the delayed initiation of treatment (> 10 days after symptom onset), the evidence suggests a potential inferiority of remdesivir (RR 1.48, 95% CI 0.45 to 4.88). However, there were no relevant subgroup differences (Chi^2= 0.74, df = 1, P = 0.39, I^2 not applicable).

Severity of condition

Three studies reported all-cause mortality by day 28 subdivided by respiratory support at baseline for 3194 participants (see Analysis 4.1). The evidence suggests a benefit for remdesivir compared to placebo or standard care alone only in the subgroup with low-flow oxygen at baseline (RR 0.32, 95% CI 0.15 to 0.66; 1 study, 435 participants; I^2 not applicable). The test for subgroup differences suggests relevant subgroup differences and reveals high heterogeneity: Chi^2 = 8.32, df = 2, P = 0.02, I^2 = 75.7%.

Duration of remdesivir application

We compared a 5-day course of remdesivir to a 10-day course for this subgroup. One study reported all-cause mortality at up to day 28 subdivided by duration of remdesivir application for 584 participants (see Analysis 5.1). Two of 191 participants receiving remdesivir for 5 days versus to 3 of 193 participants receiving remdesivir for 10 days versus 4 of 200 participants receiving control

died by day 28. There were no subgroup differences (Chi^2= 0.09, df = 1, P = 0.09, I^2 not applicable).

Sensitivity analysis

Risk of bias assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias)

We performed sensitivity analysis for the outcome clinical worsening (new need for mechanical ventilation) to explore heterogeneity (I^2 = 85% and high risk of bias in Spinner 2020). The result in effect did not differ after exclusion of Spinner 2020.

Comparison of preprints versus peer-reviewed articles

We did not include any preprints.

Comparison of premature termination of studies with completed studies

One study was stopped early because recruitment of participants was no longer possible due to infection incidences (Wang 2020). We performed sensitivity analysis for comparison of premature termination of studies with completed studies for the outcome all-cause mortality at up to day 28. The result in effect did not differ after exclusion of Wang 2020.

Comparison of adolescent and adult participants versus adult participants

One study included one participant (n = 1/562) younger than 18 years (Spinner 2020), which corresponds to 0.178% of all recruited participants in this RCT. We performed sensitivity analysis for the comparison of adolescent and adult participants versus adult participants alone in included studies and the outcome all-cause mortality at up to day 28. The result in effect did not differ after exclusion of Spinner 2020.

DISCUSSION

Summary of main results

The aim of this living systematic review was to assess the effects of remdesivir compared to placebo or standard care alone on clinical outcomes in hospitalised adults with SARS-CoV-2 infection. This is the first version of this systematic review. We included five RCTs with 7452 participants diagnosed with SARS-CoV-2 infection, of whom 3886 were randomised to receive remdesivir (Beigel 2020; Spinner 2020; Wang 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021). We identified two ongoing studies, one of which was suspended (recruitment was not possible due to infection incidences).

Remdesivir versus placebo or standard care alone

Remdesivir probably makes little or no difference to all-cause mortality at up to day 28 (RR 0.93, 95% CI 0.81 to 1.06; RD 8 fewer per 1000, 95% CI 21 fewer to 7 more; 4 studies, 7142 participants; moderate-certainty evidence).

Data on improvement in clinical status defined as liberation from respiratory support were not provided according to our outcome definition. Duration to liberation was reported in median days, which did not allow meta-analysis. Based on the available data, remdesivir may have little or no effect on the duration to liberation from invasive mechanical ventilation (Beigel 2020: 17 days versus 20 days, 1062 participants; Wang 2020: 7 days versus 15.5 days, 236 participants; low-certainty evidence). We are uncertain whether remdesivir increases or decreases the chance of clinical improvement: duration to liberation from supplemental oxygen at up to day 28 (very low-certainty evidence).

We are very uncertain whether remdesivir increases or decreases the risk of clinical worsening at up to day 28 defined by new need for mechanical ventilation (high-flow oxygen or non-invasive mechanical ventilation or invasive mechanical ventilation) (very low-certainty evidence); new need for non-invasive mechanical ventilation or high-flow oxygen (very low-certainty evidence); and new need for oxygen by mask or nasal prongs (very low-certainty evidence). We found low-certainty evidence for a decreased risk of clinical worsening in terms of new need for invasive mechanical ventilation, compared to placebo or standard care alone.

We identified subgroup differences for all-cause mortality at up to day 28 in the subgroup analysis for severity of condition, although with high heterogeneity (Chi^2 = 8.32, df = 2, P = 0.02, I^2 = 75.7%). The evidence suggests a benefit for remdesivir compared to placebo or standard care alone only in the subgroup with low-flow oxygen at baseline (RR 0.32, 95% CI 0.15 to 0.66; 1 study, 435 participants). However, these findings were based on data from one study only that reported the outcome equivalent to our predefined parameter (Beigel 2020). Data for this subgroup and outcome were not provided by any other matching study, hence uncertainty remains.

None of the included studies reported on quality of life, therefore we do not know whether remdesivir has any impact on this outcome.

We included results from three RCTs (1674 participants) to assess the adverse effects profile of remdesivir compared to placebo or standard care alone in people hospitalised with COVID-19. Remdesivir probably decreases serious adverse events (moderate-certainty evidence). We are very uncertain whether remdesivir increases or decreases adverse events (any grade) when compared to placebo or standard care alone (very low-certainty evidence).

Overall completeness and applicability of evidence

We identified five RCTs, mainly from high- and upper-middle-income countries, investigating the therapeutic effects of remdesivir in hospitalised adults with SARS-CoV-2 infection. Of 7452 total participants, 3886 were randomised to receive remdesivir. The diagnosis of SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) and, in some studies, radiological sign of COVID-19 pneumonia. The proportion of PCR-negative participants at baseline was reported in only one study (Wang 2020). The majority of participants received other experimental COVID-19 treatment options, such as corticosteroids, antimicrobials, hydroxychloroquine, convalescent plasma, or combinations of these treatments.

All the included studies involved hospitalised, moderately or severely ill people with COVID-19, or both, and compared the effect of remdesivir (3860 evaluated participants) to placebo (599 evaluated participants) or standard care alone (2944 evaluated participants). To assess the effects of remdesivir, we included data from four RCTs (7403 evaluated participants). The analysis of safety outcomes (serious adverse events, adverse events) was affected by a relevant lack of data. Since the largest study did not report safety

data (WHO Solidarity Trial Consortium 2021), we could only include data for 1674 participants from three RCTs in our analysis.

Different scales of disease severity and progression were used amongst studies, and to the present day the terms 'moderate' and 'severe' are inconsistently used to define severity of disease in different guidelines and consensus statements of national and international organisations (e.g. WHO 2020d versus WHO 2021). For hospitalised patients, the need of respiratory support essentially determines their course within the hospital (e.g. ICU admission) and, from the individual patient's perspective, has a strong impact on acute health-related quality of life, functional independence and autonomy. We therefore analysed respiratory support at baseline and during the observation period as a surrogate for COVID-19 disease severity: no oxygen, low-flow oxygen, and mechanical ventilation (including non-invasive mechanical ventilation, high-flow oxygen, and invasive mechanical ventilation). At baseline, 1957 participants did not need any additional oxygen; 4409 participants received low-flow oxygen support; and 1025 participants were treated with mechanical ventilation. Only the low-flow oxygen at baseline group showed a decreased mortality if treated with remdesivir. However, these findings were based on data from one study only (Beigel 2020). In contrast, a major subgroup comparison of participants receiving any type of oxygen (low- and high-flow) in the WHO Solidarity Trial Consortium 2021 study did not show any significant difference in 28-day mortality between remdesivir and standard care alone (n = 3639 participants; RR 0.85, 95% CI 0.66 to 1.09). Since the authors of WHO Solidarity Trial Consortium 2021 could not provide detailed data on mortality for the different levels of oxygen support, we were unable to include the reported group of low- and high-flow oxygen in our subgroup analysis. Hence, the certainty of the evidence for the effects of remdesivir in COVID-19 participants receiving low-flow oxygen at baseline remains low for methodological reasons.

We detected no differences for mortality at up to day 28 in further participant subgroups relevant for daily clinical routine, namely age, timing of first remdesivir dose, and duration of remdesivir application.

Although we contacted all study authors, especially with regard to detailed description of the extent of respiratory support (e.g. low- versus high-flow oxygen, non-invasive versus invasive mechanical ventilation), there remained differences in reporting severity of illness and incomplete data sets, resulting in a relevant obstacle to the planned subgroup analysis. Hence, due to incompleteness of the data, uncertainty remains regarding a possible benefit of remdesivir treatment for COVID-19 patients receiving low-flow oxygen support only.

Certainty of the evidence

We included data from four RCTs to assess the effects of remdesivir for individuals with moderate and severe SARS-CoV-2 infection when compared to placebo or standard care alone. We evaluated the certainty of the evidence using the GRADE approach, with any downgrading substantiated (see Summary of findings 1). The evidence for effect outcomes was of moderate to very low certainty, and the evidence for safety outcomes was of moderate to very low certainty.

All-cause mortality

We downgraded one level to moderate certainty for serious imprecision due to wide 95% confidence interval that included both benefits and harms.

Improvement of clinical status: duration to liberation from invasive mechanical ventilation

We downgraded to low certainty of evidence for serious risk of bias because of competing risk of death, and for serious imprecision because the 95% confidence interval includes both benefits and harms.

Improvement of clinical status: duration to liberation from supplemental oxygen

We downgraded to very low certainty of evidence due to serious risk of bias because of inadequate blinding of participants, personnel, and outcome assessors, and possible deviation in time point of measuring in one study, and because of competing risk of death. We also downgraded due to serious imprecision because the 95% confidence interval includes both benefits and harms, and studies reported outcomes differently because of missing standards.

Clinical worsening: new need for mechanical ventilation (high-flow oxygen, non-invasive mechanical ventilation, and invasive mechanical ventilation)

We downgraded to very low certainty because of serious imprecision due to wide confidence interval, serious inconsistency because of statistical heterogeneity, and serious risk of bias. Reasons for risk of bias were inadequate blinding of participants, personnel, and outcome assessors, as well as possible deviation in time point of measuring in one study, and competing risk of death.

Clinical worsening: new need for invasive mechanical ventilation

We downgraded to low certainty because of serious risk of bias due to inadequate blinding of participants, personnel, and outcome assessors, as well as possible deviation in time point of measuring in one study, and competing risk of death. Furthermore, studies reported outcomes differently because of missing standards.

Clinical worsening: new need for non-invasive mechanical ventilation or high-flow oxygen

We downgraded to very low certainty because of serious risk of bias due to competing risk of death, and serious imprecision due to wide confidence interval, and data coming from only one study.

Clinical worsening: new need for oxygen by mask or nasal prongs (low-flow oxygen)

We downgraded to very low certainty because of risk of bias due to competing risk of death, serious imprecision due to wide confidence interval, and data coming from only one study.

Quality of life

None of the included studies reported quality of life, therefore we do not know whether remdesivir has any impact on this outcome.

Serious adverse events

We downgraded to moderate certainty for risk of bias through competing risk of death.

Adverse events (any grade)

We downgraded to very low certainty because of serious imprecision due to wide confidence interval. We also downgraded due to serious risk of bias because of competing risk of death, and serious inconsistency due to statistical heterogeneity (I^2 = 77%).

Publication of the identified ongoing RCTs will necessitate an update of this review. The conclusions of the updated review could differ from those of the present review and may allow for a better judgment regarding the effects of remdesivir administration for the treatment of COVID-19.

Potential biases in the review process

Experienced medical information specialists of the CEOsys consortium developed an all-encompassing search strategy to identify available evidence to answer our research question. We aimed at identifying all completed, but also ongoing studies, for inclusion in this review. The sensitive search included relevant electronic databases as well as clinical trial registries. As a supplementary search, we screened reference lists of included studies. We included preprints in addition to peer-reviewed full-text articles. We are aware of the potentially lower quality of preprint publications, and that results could change once the peer-reviewed journal publications are available. Where data were missing, we contacted study authors; for details, see Characteristics of included studies. An overview of included studies is provided in Table 3. We are confident that we identified all relevant studies, and will monitor ongoing studies as well as full publication of preprints closely after the publication of this review.

Differences to review protocol

A prespecified protocol is available at an international prospective register of systematic reviews (CRD42021238065). As a major difference to the protocol, we plan a living approach for this review. Considering the current incompleteness of subgroup data regarding the effect of remdesivir for particular patient populations, we hope to reduce the uncertainty of evidence by regular updates. In contrast to our predefined inclusion criteria (adult participants), we did not exclude the study of Spinner 2020, which involved adolescent participants between 12 and 18 years. After an inquiry, we learned that only one participant (0.178%) was under the age of 18, which we presumed to have a non-relevant impact on our results. Our main outcomes were extended for data inclusion at longest follow-up for clinical status, which did not, however, exceed 28 days. Furthermore, ventilator-free days were found to be of clinical relevance after completion of the protocol and were added to the prioritised outcomes. For clinical worsening, new need for non-invasive and new need for invasive ventilation was extended by new need for low-flow oxygen to address clinical worsening relevant for the transition from ambulatory to in-hospital care. Also, after careful consideration, we decided to additionally report new need for mechanical ventilation (high-flow oxygen or non-invasive mechanical ventilation or invasive mechanical ventilation) for clinical (indication for organ dysfunction and need of intensive care) as well as patient-oriented (loss of independence and quality of life) reasons. Moreover, the combination is in accordance with the WHO definition of “severe” COVID-19 (WHO 2020d; WHO 2020e). Besides adverse events grade 3 to 4, we additionally evaluated the effect of remdesivir on adverse events of any grade to cover safety analysis regarding low-grade adverse events. We added hazard ratio to measures of effects where this information was available. Categorising into age subgroups was not possible as predefined for subgroup analysis, and we concretised disease severity according to WHO progression scale (WHO 2020d). Any change of methodology was done before analysis. We identified no other potential sources of bias in our review process.

Agreements and disagreements with other studies or reviews

The results we found do not decisively differ from those of other systematic reviews, Elsawah 2020; Piscoya 2020; Roshanshad 2020; Al-Abdouh 2021; Lai 2021; Vegivinti 2021; Welte 2021, or living guidelines (Siemieniuk 2020; Kaka 2021). Except for one review (Vegivinti 2021), which used the Scottish Intercollegiate Guidelines Network (SIGN) checklists for controlled clinical trials for the risk of bias and determination of the levels of evidence, meta-analyses and systematic reviews were conducted based on Cochrane guidelines and using the Cochrane risk of bias tool. Roshanshad 2020 used also the Newcastle-Ottawa scale for the assessment of the quality of non-randomised studies in meta-analyses. The levels of evidence were performed analogous to our review, mostly according to the GRADE approach. In contrast to our review, the cited reviews did not exclusively include RCTs with a placebo or standard care control arm, but also case studies, Elsawah 2020; Piscoya 2020; Roshanshad 2020, and simulated studies (Bansal 2021). The selection of the analysed RCTs was not always identical to that of our review. None of the other reviews cited the Mahajan 2021 study, due to its publication in March 2021. Our review excluded the publication Goldman 2020, which compared clinically used dosing schemes of remdesivir, but had no placebo or standard of care arm. The synthetic interpretation of the results of the aforementioned reviews and guidelines is difficult due to different methodological approaches, the type of subgroup formation, and the partial inclusion of non-RCTs. We found major differences in the published reviews of Kaka 2021 and Bansal 2021. Kaka 2021 found a marginally increased mortality in participants already treated with mechanical ventilation or ECMO, or both, at baseline (studies analysed: Beigel 2020; Wang 2020; WHO Solidarity Trial Consortium 2021), and a benefit for remdesivir in terms of clinical improvement (studies analysed: Beigel 2020; Spinner 2020; Wang 2020). Contrary to our findings, Bansal 2021 concluded from their meta-analysis that remdesivir significantly reduces mortality. Since the authors only included Beigel 2020, Wang 2020, and a simulated two-arm study that is only available as preprint (Hsu 2020), their conclusions are not substantiated by the entire available evidence.

AUTHORS' CONCLUSIONS

Implications for practice

We found moderate-certainty evidence that remdesivir probably has little or no effect on all-cause mortality at up to 28 days in hospitalised individuals with moderate and severe COVID-19. We were unable to perform meta-analysis of clinical improvement parameters, but considering the data provided, remdesivir may have little or no effect on the duration to liberation from invasive mechanical ventilation. We are uncertain whether remdesivir increases or decreases the chance of clinical improvement in terms of duration to liberation from supplemental oxygen at up to day 28 given the very low certainty of the evidence. We found low-certainty evidence that remdesivir may decrease the risk of new need for invasive mechanical ventilation. However, we are very uncertain

whether remdesivir affects the overall risk for clinical worsening. Remdesivir probably decreases the rate of serious adverse events; however, due to inconsistent reporting of safety data, the evidence regarding the effect of remdesivir is very uncertain when pooling any grade of adverse events. Due to incompleteness of subgroup data, we are uncertain whether there is a possible benefit of remdesivir for the treatment of COVID-19 patients receiving low-flow oxygen therapy only.

Implications for research

In this first version of a systematic review on remdesivir in hospitalised individuals with SARS-CoV-2 infection, we included data from five randomised controlled trials. Each study reported different primary outcomes. Furthermore, different scales of disease severity were applied to characterise subgroups, and safety data reporting was incomplete. These aspects lower the certainty of the evidence and make it difficult to draw valid conclusions for important clinical questions during an ongoing pandemic. In particular, differences in potential benefits or harms of remdesivir for the treatment of COVID-19 depending on disease severity could not be analysed sufficiently.

Additional data on efficacy and safety of remdesivir for different population subgroups (e.g. depending on age, severity of disease, or kidney function), timing of application of remdesivir in the course of the infection, and the establishment of core outcomes for COVID-19 research, may allow us to reduce uncertainty in potentially beneficial or harmful effects of remdesivir in future updates of this review. In accordance with the living approach of this review, we will continually update our search and include eligible trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beigel 2020

Study characteristics	
Methods	• Trial design: parallel assigned, RCT, double-blind, placebo controlled • Type of publication: journal publication • Setting: inpatient • Recruitment dates: from 21 February 2020 to 19 April 2020 • Country: the USA (45 sites), Denmark (8 sites), the UK (5 sites), Greece (4 sites), Germany (3 sites), Korea (2 sites), Mexico (2 sites), Spain (2 sites), Japan (1 site), and Singapore (1 site) • Language: English • Number of centres: 60 trial sites and 13 sub-sites • Trial registration number: NCT04280705 (ClinicalTrials.gov) • Date of trial registration: 21 February 2020

Participants	**Baseline characteristics**
	• Age (years, mean (SD)):intervention group 58.6 (14.6), control group 59.2 (15.4)
	• Gender (male, n (%)): intervention group 352 (65.1), control group 332 (63.7)
	• Race or ethnic group, intervention group vs control group (n (%)): American Indian or Alaska Native 4 (0.7) vs 3 (0.6); Asian 79 (14.6) vs 56 (10.7); black or African-American 109 (20.1) vs 117 (22.5); white 279 (51.6) vs 287 (55.1); Hispanic or Latino 134 (24.8) vs 116 (22.3)
	• Number of participants (recruited/allocated/evaluated): 1114/1062/1062;
	  * Remdesivir: intention-to-treat population 541; as-treated population 532
	  * Control: intention-to-treat population 521; as-treated population 516
	• Severity of condition according to study definition: moderate and severe COVID-19
	• Severity of condition according to WHO score: 4, 5, 6, 7, 8, 9
	• Comorbidities (intervention group vs control group (n/N (%))):
	  * Type 2 diabetes 164/532 (30.8) vs 158/519 (30.4)
	  * Hypertension 269/532 (50.6) vs 264/519 (50.9)
	  * Obesity 242/531 (45.6) vs 234/518 (45.2)
	Inclusion criteria:
	• Admitted to a hospital with symptoms suggestive of COVID-19 infection
	• Participant (or legally authorised representative) provides informed consent prior to initiation of any study procedures
	• Participant (or legally authorised representative) understands and agrees to comply with planned study procedures
	• Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
	Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either or the following:
	• PCR positive in sample collected < 72 hours prior to randomisation;

Beigel 2020 *(Continued)*

- PCR positive in sample collected ≥ 72 hours prior to randomisation, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc.) and progressive disease suggestive of ongoing SARS-CoV-2 infection.

Illness of any duration, and at least 1 of the following:

- radiographic infiltrates by imaging (chest x-ray, CT scan, etc.);
- SpO_2 ≤ 94% on room air;
- requiring supplemental oxygen;
- requiring mechanical ventilation;
- women of childbearing potential must agree to either abstinence or use at least 1 primary form of contraception not including hormonal contraception from the time of screening through day 29;
- agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through day 29.

Exclusion criteria:

- ALT or AST > 5 times the upper limit of normal
- eGFR < 30 mL/min (including individuals receiving haemodialysis or haemofiltration)
- Pregnancy or breastfeeding
- Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours
- Allergy to any study medication

Previous treatments: lopinavir/ritonavir (Kaletra)

Interventions	• Treatment details of intervention group:
	  * Remdesivir 200 mg intravenously as a loading dose on day 1, followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death
	• Treatment details of control group:
	  * The supplied placebo lyophilised formulation is identical in physical appearance to the active lyophilised formulation and contains the same inactive ingredients. Alternatively, a placebo of normal saline of equal volume may be given if there are limitations on matching placebo supplies.
	• Concomitant therapy:
	  * Supportive care according to the standard care for the trial site hospital
	  * If a hospital had a written policy or guideline for use of other treatments for COVID-19, participants could receive those treatments.
	• Treatment cross-overs: yes. After the data and safety monitoring board recommended that the preliminary primary analysis report be provided to the sponsor, data on a total of 51 participants (4.8% of the total study enrolment; 16 (3.0%) in the remdesivir group and 35 (6.7%) in the placebo group) were unblinded; 26 (74.3%) of those in the placebo group whose data were unblinded were given remdesivir. Sensitivity analyses evaluating the unblinding (participants whose treatment assignments were unblinded had their data censored at the time of unblinding) and cross-over (participants in the placebo group treated with remdesivir had their data censored at the initiation of remdesivir treatment) produced results similar to those of the primary analysis.
	• Duration of follow-up: day 29
	• Compliance with assigned treatment: yes

Outcomes	**Primary study outcome:** time to recovery: the day of recovery was defined as the first day on which the participant satisfies 1 of the following 3 categories from the ordinal scale: 1. hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care; 2. not hospitalised, limitation on activities and/or requiring home oxygen; 3. not hospitalised, no limitations on activities. **Review outcomes** Inpatient setting:

Beigel 2020 *(Continued)*

- All-cause mortality at up to day 28, day 60, time-to-event, and at hospital discharge: reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at up to day 28, day 60, and up to longest follow-up), including:
  * improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants, i.e. WHO ≤ 6, if ≥ 7 at baseline: reported, day 15;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6: NR
    - ☐ duration to liberation from invasive mechanical ventilation: reported;
    - ☐ liberation from supplemental oxygen in surviving participants, i.e. WHO ≤ 4, if ≥ 5 at baseline: reported, day 15;
    - ☐ duration to liberation from supplemental oxygen: reported.
  * worsening of clinical status:
    - ☐ new need for mechanical ventilation: reported;
    - ☐ new need for invasive mechanical ventilation: reported;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen: reported;
    - ☐ new need for oxygen by mask or nasal prongs: reported.
- Need for dialysis (at up to day 28): NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to 7 days, up to 30 days, and longest follow-up available: NR
- Admission to ICU: NR
- Duration of hospitalisation: reported
- Time to discharge from hospital: NR
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: NR
- Serious adverse events, defined as number of participants with event: reported
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: reported

Identification	
Notes	• Date of publication: 5 November 2020 • Sponsor/funding: * National Institute of Allergy and Infectious Diseases (NIAID, main sponsor) * National Cancer Institute * Department of Defence, Defence Health Program * In part funded by the governments of Denmark, Japan, Mexico, and Singapore * Gilead Sciences provided remdesivir for use in this trial but did not provide any financial support. • Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; they kindly responded and provided the requested data.

Mahajan 2021

Study characteristics

Methods	• Trial design: RCT, open-label • Type of publication: journal publication • Setting: inpatient • Recruitment dates: from June 2020 to December 2020 • Country: India • Language: English • Number of centres: 1 • Trial registration number: NR

Mahajan 2021 *(Continued)*

- Date of trial registration: NR

Participants	**Baseline characteristics**
	• Age (years, mean (SD)): intervention group 58.08 (12.1); control group 57.41 (14.1)
	• Gender (male, n (%)): intervention group 21 (61.7); control group 27 (75.0)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 82/82/70
	• Severity of condition according to study definition: moderate and severe COVID-19
	• Severity of condition according to WHO score: 5, 6
	• Comorbidities (intervention group vs control group (n/N (%))):
	  * Diabetes 21/34 (61.8) vs 21/36 (58.3)
	  * Hypothyroidism 4/34 (11.8) vs 3/36 (8.3)
	  * Hypertension 15/34 (44.1) vs 17/36 (47.2)
	  * Hyperlipidaemia 4/34 (11.8) vs 3/36 (8.3)
	  * CAD 4/34 (11.8) vs 5/36 (13.9)
	  * CKD 2/34 (5.9) vs 1/36 (2.8)
	  * Asthma 1/34 (2.9) vs 0/36 (0.0)
	Inclusion criteria
	• Adults (18 to 60 years)
	• Admitted to a hospital with moderate to severe COVID-19 with:
	  * respiratory rate > 24 per minute;
	  * radiographic evidence of pneumonia;
	  * oxygen saturation of 94% or less.
	• Has laboratory-confirmed SARS-CoV-2 infection by PCR within the last 4 days
	• Participant (or a close relative) provides written informed consent before taking part in the study
	Exclusion criteria
	• AST or ALT levels greater than 3 times the upper limit of the normal range
	• Creatinine clearance ≤ 40 mL per minute
	• Invasive mechanical ventilation
	• Multi-organ failure
	Previous treatments: NR

Interventions	• Treatment details of intervention group: 200 mg remdesivir intravenously as loading dose on day 1, followed by 100 mg remdesivir intravenously once daily for subsequent 4 days
	• Treatment details of control group: standard of care
	• Concomitant therapy: standard of care including heparin and corticosteroids; other drugs for COVID-19 treatment not allowed
	• Duration of follow-up:
	  * At least 12 days, 24 days, or until discharge or death
	  * For `time-to-recovery` and `time-to` improvement analyses, data for participants who did not recover and data for participants who died were collected at day 24.
	• Treatment cross-overs: yes; 1 participant in the control group requested remdesivir after enrolment
	• Compliance with assigned treatment: partly

Outcomes	**Primary study outcome:** clinical status from day 12 to 24 on 6 -point ordinal scale, mortality from day 12 to day 24, adverse events, admission days, changes in oxygen-support requirements, administration of high-flow oxygen, non-invasive positive pressure ventilation and invasive mechanical ventilation, hospital discharge, need for hospitalisation (if a participant was discharged before or on day 10, it was recorded as not hospitalised) **Review outcomes**

Mahajan 2021 *(Continued)*

- All-cause mortality at up to day 28, day 60, time-to-event, and at hospital discharge: NR
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at up to day 28, day 60, and up to longest follow-up, including:
  * improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants, i.e. WHO ≤ 6, if ≥ 7 at baseline: NR;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6: NR;
    - ☐ duration to liberation from invasive mechanical ventilation: NR;
    - ☐ liberation from supplemental oxygen in surviving participants, i.e. WHO ≤ 4, if ≥ 5 at baseline: NR;
    - ☐ duration to liberation from supplemental oxygen: NR.
  * worsening of clinical status:
    - ☐ new need for mechanical ventilation: NR;
    - ☐ new need for invasive mechanical ventilation: NR;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen: NR;
    - ☐ new need for oxygen by mask or nasal prongs: NR.
- Need for dialysis (at up to day 28): NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to 7 days, up to 30 days, and longest follow-up available: NR
- Admission to ICU: NR
- Duration of hospitalisation: reported
- Time to discharge from hospital: NR
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: NR
- Serious adverse events, defined as number of participants with event: NR
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: reported by authors as “any grade”

Identification	
Notes	• There is no protocol publicly available. • Date of publication: 20 March 2020 • Sponsor/funding: no information • Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; we received no response.

Spinner 2020

Study characteristics	
Methods	• Trial design: parallel assigned, randomised, controlled, open-label • Type of publication: journal publication • Setting: inpatient • Recruitment dates: from 15 March 2020 to 18 April 2020 • Countries: the USA, Europe, and Asia • Language: English • Number of centres: 105 • Trial registration number: NCT04292730 (ClinicalTrials.gov) • Date of trial registration: 3 March 2020
Participants	**Baseline characteristics** • Age (years; median (IQR)): 10-day intervention group 56 (45 to 66); 5-day intervention group 58 (48 to 66); control group 57 (45 to 66)

Spinner 2020 *(Continued)*

- Gender (male n(%)/female n (%)): 10-day intervention group 118 (61)/75 (39); 5-day intervention group 114 (60)/77 (40); control group 125 (63)/75 (38)
- Race or ethnic group (10-day intervention group/5-day intervention group/control group, n (%)): white 107 (57)/109 (59)/112 (58); black 37 (20)/35 (19)/27 (14); Asian 31 (16)/34 (18)/37 (19); other 13 (7)/8 (4)/17 (9); Hispanic or Latino ethnicity 42 (23)/25 (13)/34 (18)
- Number of participants (recruited/allocated/evaluated): 612/596/584
  * 5-day remdesivir group 199/191
  * 10-day remdesivir group 197/193
  * control group 200/200
- Severity of condition according to study definition: moderate COVID-19
- Severity of condition according to WHO score: 4 to 6
- Comorbidities (10-day intervention group/5-day intervention group/control group (n (%))):
  * Cardiovascular disease 111 (58)/111 (58)/107 (54)
  * Hypertension 85 (44)/82 (43)/81 (41)
  * Diabetes 85 (44)/71 (37)/76 (38)
  * Asthma 31 (16)/22 (12)/28 (14)

Inclusion criteria:

- Willing and able to provide written informed consent prior to performing study procedures (participants ≥ 18 years of age) or assent (participants ≥ 12 and < 18 years of age) prior to performing study procedures. For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures
- Aged ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant institutional review board or independent ethics committee)
- SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomisation
- Currently hospitalised and requiring medical care for COVID-19
- SpO_2 > 94% on room air at screening
- Radiographic evidence of pulmonary infiltrates
- Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception.

Exclusion criteria

- Participation in any other clinical trial of an experimental treatment for COVID-19
- Concurrent treatment or planned concurrent treatment with other agents with actual or possible direct-acting antiviral activity against SARS-CoV-2
- Requiring mechanical ventilation at screening
- ALT or AST > 5x upper limit of normal. If per local practice only ALT is routinely measured, exclusion criteria was evaluated on ALT alone.
- Creatinine clearance < 50 mL/min using Cockcroft-Gault formula for participants ≥ 18 years of age, and Schwartz formula for participants < 18 years of age
- Positive pregnancy test
- Breastfeeding women
- Known hypersensitivity to the study drug, the metabolites, or formulation excipient

Previous treatments: not reported

Interventions	• Treatment details of intervention group:
	  * 5-day intervention group: continued standard care therapy together with intravenous remdesivir 200 mg on day 1, followed by intravenous remdesivir 100 mg daily on days 2 to 5
	  * 10-day intervention group: continued standard care therapy together with intravenous remdesivir 200 mg on day 1, followed by intravenous remdesivir 100 mg daily on days 2 to 10
	• Treatment details of control group:
	  * Standard care (according to local guidelines)

Spinner 2020 *(Continued)*

- Concomitant therapy:
  * Concomitant use of the following is prohibited in participants receiving remdesivir:
    - ☐ Traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
    - ☐ Investigational agents with putative antiviral activity for COVID-19 including approved HIV protease inhibitors such as lopinavir/ritonavir, chloroquine, interferon, steroid, tocilizumab, azithromycin
- Duration of follow-up: day 28 (± 5 days)
- Treatment cross-overs: no
- Compliance with assigned treatment: yes

Outcomes

Primary study outcome: clinical status assessed by a 7-point ordinal scale on day 11.

- Clinical status was derived from death, hospital discharge, and ordinal scale as follows: score of 1 was used for all days on or after the date of death; score of 7 was used for all days on or after discharged-alive date; last available assessment for missing value.
  * The scale is as follows:
    a. death;
    b. hospitalised, on invasive mechanical ventilation or ECMO;
    c. hospitalised, on non-invasive ventilation or high-flow oxygen devices;
    d. hospitalised, requiring low-flow supplemental oxygen;
    e. hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
    f. hospitalised, not requiring supplemental oxygen - no longer required ongoing medical care (other than per-protocol remdesivir administration);
    g. not hospitalised.

Review outcomes

- All-cause mortality at up to day 28, day 60, time-to-event, and at hospital discharge: reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at up to day 28, day 60, and up to longest follow-up, including:
  * improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants, i.e. WHO ≤ 6, if ≥ 7 at baseline: NR;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6: NR;
    - ☐ duration to liberation from invasive mechanical ventilation: NR;
    - ☐ liberation from supplemental oxygen in surviving participants, i.e. WHO ≤ 4, if ≥ 5 at baseline: NR;
    - ☐ duration to liberation from supplemental oxygen: reported.
  * worsening of clinical status:
    - ☐ new need for mechanical ventilation: reported;
    - ☐ new need for invasive mechanical ventilation: NR;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen: NR;
    - ☐ new need for oxygen by mask or nasal prongs: NR.
- Need for dialysis (at up to day 28): NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to 7 days, up to 30 days, and longest follow-up available: NR
- Admission to ICU: NR
- Duration of hospitalisation: reported
- Time to discharge from hospital: NR
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: NR
- Serious adverse events, defined as number of participants with event: reported
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: reported (except for grade 1 to 2)

Spinner 2020 *(Continued)*

Identification	
Notes	• Date of publication: 21 August 2020 • Sponsor/funding: this study was sponsored by Gilead Sciences. • Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; they kindly responded and provided the requested data.

Wang 2020

Study characteristics	
Methods	• Trial design: parallel assigned, randomised, placebo-controlled, double-blind • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 6 February 2020 to 12 March 2020 • Country: China • Language: English • Number of centres: 10 • Trial registration number: NCT04257656 (ClinicalTrials.gov) • Date of trial registration: 31 January 2020

Participants	**Baseline characteristics**
	• Age (years, median (IQR)): intervention group: 66.0 (57.0 to 73.0), control group: 64.0 (53.0 to 70.0)
	• Gender (male/female, n (%)): intervention group: 89 (56)/69 (44), control group: 51 (65)/27 (35)
	• Ethnicity: not reported
	• Number of participants (recruited/allocated/evaluated): 236/intervention group: 158, control group: 78
	• Severity of condition according to study definition: severe COVID-19
	• Severity of condition according to WHO score: WHO 4 to 10 (10-point scale)
	• Comorbidities (intervention group vs control group, (n (%))):
	  * Hypertension 72 (46) vs 30 (38)
	  * Diabetes 40 (25) vs 16 (21)
	  * Coronary heart disease 15 (9) vs 2 (3)
	Inclusion criteria
	• Age ≥ 18 years at time of signing of informed consent form
	• Laboratory (RT-PCR)-confirmed COVID-19
	• Pneumonia confirmed by chest imaging
	• Oxygen saturation (SaO_2/SpO_2) ≤ 94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio < 300 mmHg
	• ≤ 12 days of symptom onset
	• Willingness of study participant to accept randomisation to any assigned treatment arm
	• Eligible participants of child-bearing age (men and women) agreed to take effective contraceptive measures (including hormonal contraception, barrier methods, or abstinence) during the study period and for at least 7 days after the last study drug administration
	• Participants must agree not to enrol in any other study of an antiviral agent prior to completing the 28-day follow-up.
	Exclusion criteria:

Wang 2020 *(Continued)*

- Physician decides that trial involvement is not in the patient's best interest, or any condition that does not allow the protocol to be followed safely
- Severe liver disease (e.g. Child-Pugh score ≥ C, AST > 5 times upper limit)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Patients with known severe renal impairment (eGFR ≤ 30 mL/min/1.73 m^2) or receiving continuous renal replacement therapy, haemodialysis, peritoneal dialysis
- Will be transferred to another hospital which is not the study site within 72 hours
- Receipt of any experimental treatment for COVID-19 within the 30 days prior to the time of the screening evaluation

Previous treatments (received before and after enrolment): injection of interferon alfa-2b; lopinavir–ritonavir; vasopressors; renal replacement therapy; antibiotics; corticosteroids

Interventions

- Treatment details of intervention group: remdesivir
  - Loading dose: 200 mg in 350 mL normal saline (0.9% sodium chloride) intravenous on day 1
  - Maintenance doses: 100 mg in 250 mL normal saline (0.9% sodium chloride) intravenous once daily on days 2 to 10.
- Treatment details of control group: placebo infusions
  - Loading dose: in 350 mL normal saline (0.9% sodium chloride) intravenous on day 1
  - Maintenance doses: 250 mL normal saline (0.9% sodium chloride) intravenous once daily on days 2 to 10
- Concomitant therapy: concomitant use of the following:
  - Lopinavir–ritonavir
  - Interferon alfa-2b
  - Antibiotics
  - Corticosteroids
  - No information about standard of care
- Treatment cross-overs: no
- Duration of follow-up: day 28
- Compliance with assigned treatment: yes

Outcomes

Primary study outcome: time to clinical improvement at up to day 28. Clinical improvement was defined as a 2-point reduction in participant's admission status on a 6-point ordinal scale, or live discharge from the hospital, whichever came first. The scale is as follows: 6. death; 5. hospital admission for ECMO or mechanical ventilation; 4. hospital admission for non-invasive ventilation or high-flow oxygen therapy; 3. hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation); 2. hospital admission but not requiring oxygen therapy; 1. discharged or having reached discharge criteria (defined as clinical recovery, i.e. normalisation of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hours).

Review outcomes

Inpatient setting:

- All-cause mortality at up to day 28, day 60, time-to-event, and at hospital discharge: reported

Wang 2020 *(Continued)*

- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at up to day 28, day 60, and up to longest follow-up), including:
  * improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants, i.e. WHO ≤ 6, if ≥ 7 at baseline: NR;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6: NR;
    - ☐ duration to liberation from invasive mechanical ventilation: reported;
    - ☐ liberation from supplemental oxygen in surviving participants, i.e. WHO ≤ 4, if ≥ 5 at baseline: NR;
    - ☐ duration to liberation from supplemental oxygen: reported.
  * worsening of clinical status:
    - ☐ new need for mechanical ventilation: NR;
    - ☐ new need for invasive mechanical ventilation: NR;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen: NR;
    - ☐ new need for oxygen by mask or nasal prongs: NR.
- Need for dialysis (at up to day 28): NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to 7 days, up to 30 days, and longest follow-up available: NR
- Admission to ICU: NR
- Duration of hospitalisation: reported
- Time to discharge from hospital: reported
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: reported
- Serious adverse events, defined as number of participants with event: reported
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: reported

Identification	
Notes	• Date of publication: 29 April 2020 • Sponsor/funding: * This study was funded by Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing science and technology project. * Remdesivir or placebo infusions for a total of 10 days were both provided by Gilead Sciences, Foster City, CA, USA. • Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; we did not receive a response.

WHO Solidarity Trial Consortium 2021

Study characteristics

Methods	• Trial design: RCT, open-label • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 22 March 2020 to 4 October 2020 • Country: Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, Switzerland, Canada, Argentina, Brazil, Colombia, Honduras, Peru, Egypt, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Pakistan, the Philippines, Saudi Arabia, South Africa • Language: English • Number of centres: 405 • Trial registration number: NCT04315948 (ClinicalTrials.gov); ISRCTN83971151 (ISRCTN registry)

WHO Solidarity Trial Consortium 2021 *(Continued)*

- Date of trial registration: 20 March 2020

Participants	**Baseline characteristics**
	• Age (years, n intervention group vs n control group) < 50 years, 961 vs 952; 50 to 69 years, 1282 vs 1287; ≥ 70 years, 500 vs 469
	• Gender (male, n): intervention group 1706 (62.19%); control group 1725 (63.70%)
	• Ethnicity (geographic region, n intervention group vs n control group): Europe and Canada 715 vs 698; Latin America 470 vs 514; Asia and Africa 1558 vs 1496
	• Number of participants (recruited/allocated/evaluated): 11266 (remdesivir group 2743, control group 2708)
	• Severity of condition according to study definition: no supplemental oxygen at entry, supplemental oxygen at entry, already receiving ventilation
	• Severity of condition according to WHO score: 4, 5, ≥ 6
	• Comorbidities (intervention group vs control group (n (%))):
	  * Diabetes 707 (25.8) vs 666 (24.6)
	  * Heart disease 571 (20.8) vs 567 (20.9)
	  * Chronic lung disease 151 (5.5) vs 145 (5.4)
	  * Asthma 139 (5.1) vs 139 (5.1)
	  * Chronic liver disease 36 (1.3) vs 41 (1.5)
	Inclusion criteria:
	• Adults (aged ≥ 18 years) hospitalised with definite COVID-19
	• Not already receiving any of the study drugs
	• Without known allergy or contraindications to any of the study drugs (in the view of the physician responsible for their care)
	• Without anticipated transfer within 72 h to a non-study hospital
	Exclusion criteria:
	• Refusal to participate expressed by patient or legally authorised representative if they are present
	• Spontaneous blood ALT/AST levels > 5 times the upper limit of normal
	• Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/min)
	• Pregnancy or breastfeeding
	• Anticipated transfer to another hospital which is not a study site within 72 hours
	• Patients previously treated with 1 of the antivirals evaluated in the trial (i.e. remdesivir, interferon beta-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days
	• Contraindication to any study medication including allergy
	Previous treatments: NR

Interventions	• Treatment details of intervention group:
	  * Remdesivir was administered as a 200 mg intravenous loading dose on day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalisation up to a 10-day total course, plus local standard care.
	• Treatment details of control group:
	  * The controls were patients assigned to the standard care at a time and place in which drug was locally available.
	• Concomitant therapy: local SoC
	• Treatment cross-overs: no
	• Duration of follow-up: day 28
	• Compliance with assigned treatment: yes

Outcomes	**Primary study outcome:** all-cause mortality, subdivided by the severity of disease at the time of randomisation, measured using patient records throughout the study

WHO Solidarity Trial Consortium 2021 *(Continued)*

Review outcomes

- All-cause mortality at up to day 28, day 60, time-to-event, and at hospital discharge: reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at up to day 28, day 60, and up to longest follow-up), including:
  * improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants, i.e. WHO ≤ 6, if ≥ 7 at baseline: NR;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6: NR;
    - ☐ duration to liberation from invasive mechanical ventilation: NR;
    - ☐ liberation from supplemental oxygen in surviving participants, i.e. WHO ≤ 4, if ≥ 5 at baseline: NR;
    - ☐ duration to liberation from supplemental oxygen: NR.
  * worsening of clinical status:
    - ☐ new need for mechanical ventilation: reported;
    - ☐ new need for invasive mechanical ventilation: NR;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen: NR;
    - ☐ new need for oxygen by mask or nasal prongs: NR.
- Need for dialysis (at up to day 28): NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to 7 days, up to 30 days, and longest follow-up available: NR
- Admission to ICU: NR
- Duration of hospitalisation: reported, data not useable
- Time to discharge from hospital: NR
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: NR
- Serious adverse events, defined as number of participants with event: NR
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: NR

Identification	
Notes	• Date of publication: 2 December 2020 • Sponsor/funding: in each country the co-sponsors of this study are the National Ministry of Health and the WHO. • Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; they kindly responded that there were no additional data to provide.

Abbreviations:
ALT = alanine transaminase
AST = aspartate transaminase
CAD = coronary artery disease
CKD = chronic kidney disease
CT = computed tomography
ECMO = extracorporeal membrane oxygenation
eGFR = estimated glomerular filtration rate
HR = hazard ratio
ICU = intensive care unit
IQR = interquartile range
IWRS = interactive web response system
N = total number of participants
n = number of participants
NA = not applicable
NR = not reported
NEWS = National Early Warning Score
NIAID = National Institute of Allergy and Infectious Diseases
OR = odd ratio
PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen

PCR = polymerase chain reaction
RCT = randomised controlled trial
RT-PCR = reverse transcription polymerase chain reaction
SaO_2 = arterial oxygen saturation
SD = standard deviation
SoC = standard of care
SpO_2 = peripheral oxygen saturation
ULN = upper limit of normal
WHO = World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ader 2020	Duplicate
Ader 2021	No data about the remdesivir intervention
Alpern 2020	Not a randomised controlled trial
Antinori 2020	Not a randomised controlled trial
Banerjee 2020	Not a randomised controlled trial
CTRI/2020/12/029613	No intervention with remdesivir
CTRI/2020/12/029615	Combination of remdesivir with other treatments
Deresinski 2020	Not a randomised controlled trial
Elliott 2020	Not a randomised controlled trial
Elliott 2021	Combination of remdesivir with other treatments
EUCTR2020-000841-15-ES	Intervention with remdesivir not compared to standard care or placebo
EUCTR2020-000936-23	Duplicate
Euctr2020-003510-12-dk	Wrong patient population
EUCTR2020-004928-42-HU	Wrong patient population
Goldberg 2021	Not a randomised controlled trial
Goldman 2020	Combination of remdesivir with other treatments
Goldman 2020a	Intervention with remdesivir not compared to standard care or placebo
ISRCTN15874265	Combination of remdesivir with other treatments
ISRCTN85762140	Wrong patient population
Jang 2021	Combination of remdesivir with other treatments
Kalil 2021	Combination of remdesivir with other treatments
Lapadula 2020	Not a randomised controlled trial

Study	Reason for exclusion
LBCTR2020043495	Duplicate
Medical Brief	Full-text not retrievable
NCT04252664a	Duplicate
NCT04256395	Not a randomised controlled trial
NCT04280705	Duplicate
NCT04292899	Combination of remdesivir with other treatments
NCT04302766	Wrong patient population
NCT04321928	No intervention with remdesivir
NCT04323761	Wrong patient population
NCT04353596	No intervetion with remdesivir
NCT04401579	Combination of remdesivir with other treatments
NCT04409262	Combination of remdesivir with other treatments
NCT04410354	Combination of remdesivir with other treatments
NCT04480333	Wrong patient population
NCT04488081	Combination of remdesivir with other treatments
NCT04492475	Combination of remdesivir with other treatments
NCT04501952	Wrong patient population
NCT04501978	Combination of remdesivir with other treatments
NCT04539262	Wrong patient population
NCT04583956	Combination of remdesivir with other treatments
NCT04583969	Combination of remdesivir with other treatments
NCT04640168	Combination of remdesivir with other treatments
NCT04647695	Combination of remdesivir with other treatments
NCT04678739	Combination of remdesivir with other treatments
NCT04693026	Combination of remdesivir with other treatments
NCT04713176	Combination of remdesivir with other treatments
NCT04728880	Not a randomised controlled trial
Olender 2020	Intervention with remdesivir not compared to standard care or placebo

Study	Reason for exclusion
Pan 2020	Duplicate
Pan 2021	Duplicate
Saito 2020	Not a randomised controlled trial
Shih 2020	Not a randomised controlled trial
Soto 2020	Not a randomised controlled trial
Sun 2020	Not a randomised contolled trial
Tran 2020	Not a randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT04252664

Study name	A trial of remdesivir in adults with mild and moderate COVID-19
Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment • Masking: quadruple (participant, care provider, investigator, outcomes assessor) • Primary purpose: treatment Sample size: NR • Estimated enrolment: 308 participants Setting: inpatient Language: Chinese Number of centres: 1 (Jin Yin-tan hospital Wuhan, Hubei, China, 100013) Type of intervention: drug

Participants	**Inclusion criteria:**
	• Age ≥ 18 years at time of signing Informed Consent Form
	• Laboratory (RT-PCR)-confirmed COVID-19
	• Lung involvement confirmed with chest imaging
	• Hospitalised with:
	  * fever ≥ 36.7 °C axilla or oral temperature ≥ 38.0 °C or ≥ 38.6 °C tympanic or rectal or
	  * and at least 1 of respiratory rate > 24/min or cough.
	• ≤ 8 days since illness onset
	• Willingness of study participant to accept randomisation to any assigned treatment arm
	• Must agree not to enrol in another study of an investigational agent prior to completion of day 28 of study
	Exclusion criteria:
	• Physician decides that trial involvement is not in patient's best interest, or any condition that does not allow the protocol to be followed safely

NCT04252664 *(Continued)*

- Severe liver disease (e.g. Child-Pugh score ≥ C, AST > 5 times upper limit)
- $SaO_2/SPO_2 \leq 94\%$ in room air condition, or PaO_2/FiO_2 ratio < 300 mmHg
- Known allergic reaction to remdesivir
- Patients with known severe renal impairment (eGFR ≤ 30 mL/min/1.73 m^2) or receiving continuous renal replacement therapy, haemodialysis, peritoneal dialysis
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Will be transferred to another hospital which is not the study site within 72 hours
- Receipt of any experimental treatment for COVID-19 within the 30 days prior to the time of the screening evaluation

Interventions

Details of intervention:

- Drug: remdesivir (other name: GS-5734)
  - Dose: RDV 200 mg loading dose (day 1), 100 mg (once daily, 9 days) maintenance doses
  - Route of administration: intravenous

Treatment details of control group (e.g. dose, route of administration):

- Drug: remdesivir placebo
  - Dose: RDV placebo 200 mg loading dose (day 1), 100 mg (once daily, 9 days) maintenance dose
  - Route of administration: intravenous

Concomitant therapy: NR

Outcomes

Primary study outcome:

Time to clinical recovery (TTCR) [time frame: up to 28 days]

TTCR is defined as the time (in hours) from initiation of study treatment (active or placebo) until normalisation of fever, respiratory rate, and oxygen saturation, and alleviation of cough, sustained for at least 72 hours, or live hospital discharge, whichever comes first.

Normalisation and alleviation criteria:

- Fever: < 37 °C
- Respiratory rate: ≤ 24/min on room air
- Oxygen saturation: > 94% on room air
- Cough: mild or absent on a patient-reported scale of severe, moderate, mild, absent

Secondary outcome measures:

- All-cause mortality [Time Frame: up to 28 days]
  - Baseline SpO_2 during screening, PaO_2/FiO_2 < 300 mmHg or a respiratory rate ≥ 24 breaths per minute without supplemental oxygen
- Frequency of respiratory progression [Time Frame: up to 28 days]
  - Defined as $SpO_2 \leq 94\%$ on room air or PaO_2/FiO_2 < 300 mmHg and requirement for supplemental oxygen or more advanced ventilator support
- Time to defervescence (in those with fever at enrolment) [Time Frame: up to 28 days]
- Time to cough reported as mild or absent (in those with cough at enrolment rated severe or moderate) [Time Frame: up to 28 days]
- Time to dyspnoea reported as mild or absent (on a scale of severe, moderate, mild absent, in those with dyspnoea at enrolment rated as severe or moderate) [Time Frame: up to 28 days]
- Frequency of requirement for supplemental oxygen or non-invasive ventilation [Time Frame: up to 28 days]
- Time to 2019-nCoV RT-PCR negative in upper respiratory tract specimen [Time Frame: up to 28 days]
- Change (reduction) in 2019-nCoV viral load in upper respiratory tract specimen as assessed by area under viral load curve [Time Frame: up to 28 days]
- Frequency of requirement for mechanical ventilation [Time Frame: up to 28 days]

NCT04252664 *(Continued)*

- Frequency of serious adverse events [Time Frame: up to 28 days]

Review outcomes:

Inpatient setting:

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: planned
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at day 28, day 60, and up to longest follow-up), including:
  * improvement of clinical status: planned:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants, i.e. WHO ≤ 6, if ≥ 7 at baseline;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving participants, i.e. WHO ≤ 4, if ≥ 5 at baseline;
    - ☐ duration to liberation from supplemental oxygen.
  * worsening of clinical status: planned:
    - ☐ new need for mechanical ventilation;
    - ☐ new need for invasive mechanical ventilation;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen;
    - ☐ new need for oxygen by mask or nasal prongs.
- Need for dialysis (at up to 28 days): not planned
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available: not planned
- Admission to ICU: not planned
- Duration of hospitalisation: planned
- Time to discharge from hospital: planned
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: planned
- Vitamin D serum levels: not planned
- Serious adverse events, defined as number of participants with event: planned
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: not planned

Starting date	12 February 2020
Contact information	Bin Cao, China-Japan Friendship Hospital
Notes	• Recruitment status: suspended, "The epidemic of COVID-19 has been controlled well at present, no eligible patients can be recruited." • Prospective completion date: 10 April 2020 • Date last update was posted: 15 April 2020 • Sponsor/funding: Capital Medical University

NCT04596839

Study name	Antiviral activity and safety of remdesivir in Bangladeshi patients with severe coronavirus disease (COVID-19)
Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment

NCT04596839 *(Continued)*

- Masking: none (open-label)
- Primary purpose: treatment

Sample size: NR

- Estimated enrolment: 60 participants

Setting: inpatient

Language: Bengali

Number of centres: 1 (Combined Military Hospital Dhaka, Bangladesh, 1206)

Type of intervention: drug

Participants	**Inclusion criteria:**
	• Age ≥ 18 years at time of signing Informed Consent Form
	• Hospitalised with diagnosed COVID-19 confirmed by RT-PCR test ≤ 7 days before randomisation with any 1 following criteria:
	  * Respiratory distress (≥ 30 breaths/min)
	  * Finger oxygen saturation ≤ 93% at rest
	  * Arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg
	• Willingness of study participant to accept randomisation to any assigned treatment arm
	• Must agree not to enrol in another study of an investigational agent prior to completion of day 28 of study
	Exclusion criteria:
	• Physician decides that trial involvement is not in patient's best interest, or any condition that does not allow the protocol to be followed safely
	• Severe liver disease (ALT or AST > 5 times the upper limit of normal)
	• eGFR < 30 mL/min (including patients receiving haemodialysis or haemofiltration)
	• Mechanically ventilated (including venovenous ECMO) ≥ 5 days, or any duration of venoarterial ECMO
	• Known hypersensitivity to the remdesivir, the metabolites, or formulation excipient
	• Pregnancy or breastfeeding
	• Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours

Interventions	• Details of intervention:
	  * SoC + RDV 200 mg (day 1)/RDV 100 mg (days 2, 3, 4, and 5)
	  * Remdesivir INN 100 mg lyophilised powder for infusion
	• Treatment details of control group (e.g. dose, route of administration):
	  * SoC
	  * Standard care treatment for COVID-19 Infection
	• Concomitant therapy: NR

Outcomes	Primary study outcome:
	• Duration of hospital stay (days) [Time Frame: 28 days]
	Secondary study outcomes:
	• Time to clinical improvement [Time Frame: 28 days]. Time to clinical improvement (censored at day 28), defined as the time (in days) from randomisation of study treatment until a decline of 2 categories on a 6-category ordinal scale of clinical status (1 = discharged; 6 = death) or live discharge from hospital. 6-category ordinal scale:
	  * Hospital discharge or meets discharge criteria
	  * Hospitalisation, not requiring supplemental oxygen

NCT04596839 *(Continued)*

  * Hospitalisation, requiring supplemental oxygen (but not non-invasive ventilation/high-flow nasal cannula)
  * ICU/hospitalisation, requiring non-invasive ventilation/high-flow nasal cannula therapy
  * ICU, requiring ECMO and/or invasive mechanical ventilation
  * Death
- All causes mortality [Time Frame: 28 days]
- Duration (days) of mechanical ventilation [Time Frame: 28 days]
- Duration (days) of supplemental oxygenation [Time Frame: 28 days]
- Time to 2019-nCoV RT-PCR negativity in nasopharyngeal swab [Time Frame: 28 days]
- Frequency of serious adverse drug events [Time Frame: 28 days]

Review outcomes

Inpatient setting:

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: planned
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at day 28, day 60, and up to longest follow-up), including:
  * improvement of clinical status: planned:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants;
    - ☐ ventilator-free days;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving participants;
    - ☐ duration to liberation from supplemental oxygen.
  * Worsening of clinical status: not planned:
    - ☐ new need for mechanical ventilation;
    - ☐ new need for invasive mechanical ventilation;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen;
    - ☐ new need for oxygen by mask or nasal prongs.
- Need for dialysis (at up to 28 days): not planned
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available: not planned
- Admission to ICU: planned
- Duration of hospitalisation: planned
- Time to discharge from hospital: planned
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: planned
- Vitamin D serum levels: not planned
- Serious adverse events, defined as number of participants with event: planned
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: not planned

Starting date	4 September 2020
Contact information	Dr Md. Alimur Reza, MBBS, MPH +8801711438139 NCT04596839,%20BEX-06001,%20Antiviral%20Activity%20and%20Safety%20of%20Remdesivir%20in%20Bangladeshi%20Patients%20With%20Severe%20Coronavirus%20Disease%20(COVID-19)" type="EXTERNAL">rea@bpl.net
Notes	• Recruitment status: recruiting • Prospective completion date: 30 April 2021 • Date last update was posted: 27 January 2021 • Sponsor/funding: Dr Md. Alimur Reza, Beximco Pharmaceuticals Ltd.

Abbreviations
ALT = alanine transaminase
AST = aspartate transaminase
ECMO = extracorporeal membrane oxygenation
eGFR = estimated glomerular filtration rate
ICU = intensive care unit
NIAID = National Institute of Allergy and Infectious Diseases
NR = not reported
PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen
PCR = polymerase chain reaction
RCT = randomised controlled trial
RDV = remdesivir
RT-PCR = reverse transcription polymerase chain reaction
SaO_2 = arterial oxygen saturation
SAE = serious adverse events
SoC = standard of care
WHO = World Health Organization

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✓	✓	✓
Wang 2020	~	✓	✓	✓	✓	~
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.2 All-cause mortality at hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.3 All-cause mortality (time-to-event)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Worsening of clinical status: new need for mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 WHO 6 to 9 at day 28 (± 1 day), if ≤5 at baseline						
Beigel 2020	✓	✓	~	✓	✓	~
Spinner 2020	✓	✓	~	✗	✓	✗
WHO Solidarity Trial Consortium 2021	✓	✓	~	✓	~	~

Risk of bias for analysis 1.5 Worsening of clinical status: new need for invasive mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.5.1 WHO 7 to 9 at day 28 (± 1 day), if ≤6 at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✗	✓	✗

Risk of bias for analysis 1.6 Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.6.1 WHO= 6 at day 29, if ≤5 at baseline						
Beigel 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.7 Worsening of clinical status: new need for oxygen by mask or nasal prongs

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.7.1 WHO= 5 at day 29, if ≤ 4 at baseline						
Beigel 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.8 Viral clearance

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.8.1 Viral clearance at baseline						
Wang 2020	~	✓	✗	✓	✗	✗
Subgroup 1.8.2 Viral clearance at day 3						
Wang 2020	~	✓	✗	✓	✗	✗
Subgroup 1.8.3 Viral clearance at day 7						
Wang 2020	~	✓	✗	✓	✗	✗
Subgroup 1.8.4 Viral clearance at day 14						
Wang 2020	~	✓	✗	✓	✗	✗

Risk of bias for analysis 1.9 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	✓	✓	~
Wang 2020	~	✓	~	✓	✓	~

Risk of bias for analysis 1.10 Adverse events, any grade

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	~	✓	~
Wang 2020	~	✓	~	✓	✓	~

Risk of bias for analysis 1.11 Adverse events, grade 3 to 4

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	✓	~	~
Wang 2020	~	✓	~	✓	✓	~

Risk of bias for analysis 2.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 Age <50 years						
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓
Subgroup 2.1.2 Age 50 to 69 years						
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓
Subgroup 2.1.3 Age >69 years						
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.1.1 ≤ 10 days of symptom onset						
Wang 2020	~	✓	✓	✓	✓	~
Subgroup 3.1.2 > 10 days of symptom onset						
Wang 2020	~	✓	✓	✓	✓	~

Risk of bias for analysis 4.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.1.1 No oxygen at baseline						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓
Subgroup 4.1.2 Low-flow oxygen at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
Subgroup 4.1.3 Mechanical ventilation at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.1.1 5-day remdesivir						
Spinner 2020	✓	✓	✓	✓	✓	✓
Subgroup 5.1.2 10-day remdesivir						
Spinner 2020	✓	✓	✓	✓	✓	✓

DATA AND ANALYSES

Comparison 1. Remdesivir versus placebo or standard care alone

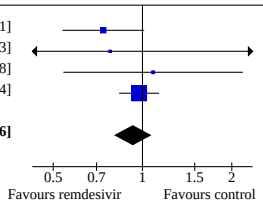
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at up to day 28	4	7142	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.06]
1.2 All-cause mortality at hospital discharge	1	5451	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.14]
1.3 All-cause mortality (time-to-event)	2	6513	Hazard Ratio (IV, Fixed, 95% CI)	0.93 [0.80, 1.07]
1.4 Worsening of clinical status: new need for mechanical ventilation	3	6696	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.48, 1.24]
1.4.1 WHO 6 to 9 at day 28 (± 1 day), if ≤5 at baseline	3	6696	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.48, 1.24]
1.5 Worsening of clinical status: new need for invasive mechanical ventilation	2	1159	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.41, 0.77]
1.5.1 WHO 7 to 9 at day 28 (± 1 day), if ≤6 at baseline	2	1159	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.41, 0.77]
1.6 Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen	1	573	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.98]
1.6.1 WHO= 6 at day 29, if ≤5 at baseline	1	573	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.98]
1.7 Worsening of clinical status: new need for oxygen by mask or nasal prongs	1	138	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.54, 1.22]
1.7.1 WHO= 5 at day 29, if ≤ 4 at baseline	1	138	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.54, 1.22]
1.8 Viral clearance	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 Viral clearance at baseline	1	196	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.50, 1.68]
1.8.2 Viral clearance at day 3	1	196	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.61, 1.54]
1.8.3 Viral clearance at day 7	1	196	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.38]
1.8.4 Viral clearance at day 14	1	196	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.12]
1.9 Serious adverse events	3	1674	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.63, 0.90]

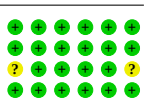
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10 Adverse events, any grade	3	1674	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.86, 1.27]
1.11 Adverse events, grade 3 to 4	3	1674	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.00]

Analysis 1.1. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 1: All-cause mortality at up to day 28

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Beigel 2020	59	541	77	521	18.3%	0.74 [0.54 , 1.01]
Spinner 2020	3	193	4	200	0.8%	0.78 [0.18 , 3.43]
Wang 2020	22	158	10	78	3.8%	1.09 [0.54 , 2.18]
WHO Solidarity Trial Consortium 2021	285	2743	289	2708	77.0%	0.97 [0.83 , 1.14]
Total (95% CI)		**3635**		**3507**	**100.0%**	**0.93 [0.81 , 1.06]**
Total events:	369		380			

Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



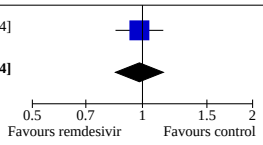


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality at up to day 28
(C) Bias due to missing outcome data: All-cause mortality at up to day 28
(D) Bias in measurement of the outcome: All-cause mortality at up to day 28
(E) Bias in selection of the reported result: All-cause mortality at up to day 28
(F) Overall bias: All-cause mortality at up to day 28

Analysis 1.2. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 2: All-cause mortality at hospital discharge

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI
WHO Solidarity Trial Consortium 2021	301	2743	303	2708	100.0%	0.98 [0.84 , 1.14]
Total (95% CI)		**2743**		**2708**	**100.0%**	**0.98 [0.84 , 1.14]**
Total events:	301		303			

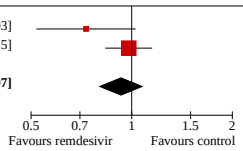
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality at hospital discharge
(C) Bias due to missing outcome data: All-cause mortality at hospital discharge
(D) Bias in measurement of the outcome: All-cause mortality at hospital discharge
(E) Bias in selection of the reported result: All-cause mortality at hospital discharge
(F) Overall bias: All-cause mortality at hospital discharge

Analysis 1.3. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 3: All-cause mortality (time-to-event)

Study or Subgroup	log[Hazard Ratio]	SE	Remdesivir Total	Placebo or standard care alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F
Beigel 2020	-0.314711	0.174362	541	521	18.2%	0.73 [0.52 , 1.03]		+ + + + + +
WHO Solidarity Trial Consortium 2021	-0.020203	0.082342	2743	2708	81.8%	0.98 [0.83 , 1.15]		+ + + + + +
Total (95% CI)			**3284**	**3229**	**100.0%**	**0.93 [0.80 , 1.07]**		

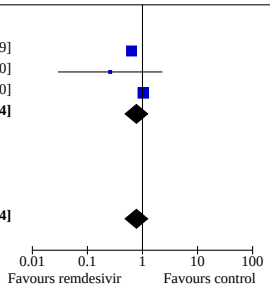


Heterogeneity: Chi² = 2.33, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality (time-to-event)
(C) Bias due to missing outcome data: All-cause mortality (time-to-event)
(D) Bias in measurement of the outcome: All-cause mortality (time-to-event)
(E) Bias in selection of the reported result: All-cause mortality (time-to-event)
(F) Overall bias: All-cause mortality (time-to-event)

Analysis 1.4. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 4: Worsening of clinical status: new need for mechanical ventilation

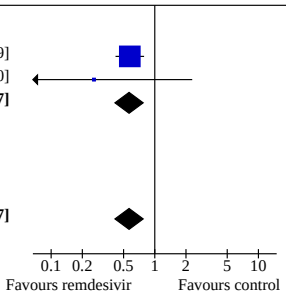
Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.4.1 WHO 6 to 9 at day 28 (± 1 day), if ≤5 at baseline								
Beigel 2020	104	709	146	630	46.4%	0.63 [0.50 , 0.79]		+ + ? + + ?
Spinner 2020	1	193	4	200	4.3%	0.26 [0.03 , 2.30]		+ + ? - + -
WHO Solidarity Trial Consortium 2021	295	2489	284	2475	49.3%	1.03 [0.89 , 1.20]		+ + ? + ? ?
Subtotal (95% CI)		**3391**		**3305**	**100.0%**	**0.78 [0.48 , 1.24]**		
Total events:	400		434					
Heterogeneity: Tau² = 0.11; Chi² = 13.47, df = 2 (P = 0.001); I² = 85%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Total (95% CI)		**3391**		**3305**	**100.0%**	**0.78 [0.48 , 1.24]**		
Total events:	400		434					
Heterogeneity: Tau² = 0.11; Chi² = 13.47, df = 2 (P = 0.001); I² = 85%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status: new need for mechanical ventilation
(C) Bias due to missing outcome data: Worsening of clinical status: new need for mechanical ventilation
(D) Bias in measurement of the outcome: Worsening of clinical status: new need for mechanical ventilation
(E) Bias in selection of the reported result: Worsening of clinical status: new need for mechanical ventilation
(F) Overall bias: Worsening of clinical status: new need for mechanical ventilation

Analysis 1.5. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 5: Worsening of clinical status: new need for invasive mechanical ventilation

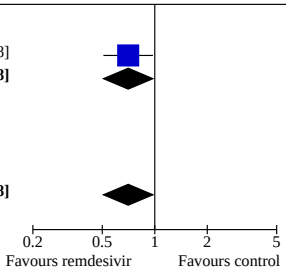
Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.5.1 WHO 7 to 9 at day 28 (± 1 day), if ≤6 at baseline							
Beigel 2020	52	402	82	364	97.9%	0.57 [0.42 , 0.79]	+ + + + + +
Spinner 2020	1	193	4	200	2.1%	0.26 [0.03 , 2.30]	+ + + - + -
Subtotal (95% CI)		**595**		**564**	**100.0%**	**0.56 [0.41 , 0.77]**	
Total events:	53		86				
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%							
Test for overall effect: Z = 3.57 (P = 0.0004)							
Total (95% CI)		**595**		**564**	**100.0%**	**0.56 [0.41 , 0.77]**	
Total events:	53		86				
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%							
Test for overall effect: Z = 3.57 (P = 0.0004)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status: new need for invasive mechanical ventilation
(C) Bias due to missing outcome data: Worsening of clinical status: new need for invasive mechanical ventilation
(D) Bias in measurement of the outcome: Worsening of clinical status: new need for invasive mechanical ventilation
(E) Bias in selection of the reported result: Worsening of clinical status: new need for invasive mechanical ventilation
(F) Overall bias: Worsening of clinical status: new need for invasive mechanical ventilation

Analysis 1.6. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 6: Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen

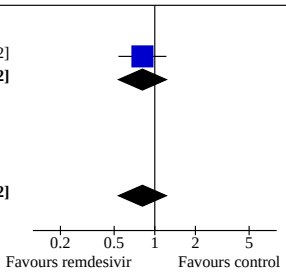
Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.6.1 WHO= 6 at day 29, if ≤5 at baseline							
Beigel 2020	52	307	64	266	100.0%	0.70 [0.51 , 0.98]	+ + ? + + ?
Subtotal (95% CI)		**307**		**266**	**100.0%**	**0.70 [0.51 , 0.98]**	
Total events:	52		64				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.10 (P = 0.04)							
Total (95% CI)		**307**		**266**	**100.0%**	**0.70 [0.51 , 0.98]**	
Total events:	52		64				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.10 (P = 0.04)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen
(C) Bias due to missing outcome data: Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen
(D) Bias in measurement of the outcome: Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen
(E) Bias in selection of the reported result: Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen
(F) Overall bias: Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen

Analysis 1.7. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 7: Worsening of clinical status: new need for oxygen by mask or nasal prongs

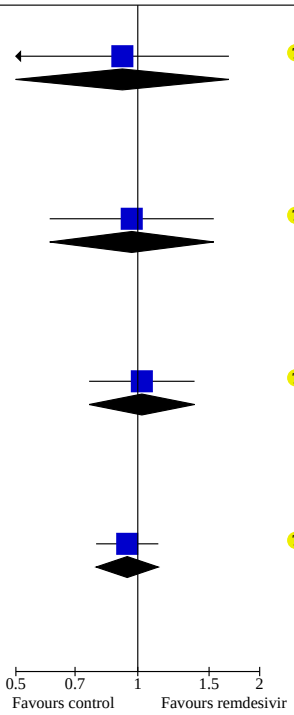
Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.7.1 WHO= 5 at day 29, if ≤ 4 at baseline												
Beigel 2020	27	75	28	63	100.0%	0.81 [0.54 , 1.22]	+	+	?	+	+	?
Subtotal (95% CI)		**75**		**63**	**100.0%**	**0.81 [0.54 , 1.22]**						
Total events:	27		28									
Heterogeneity: Not applicable												
Test for overall effect: Z = 1.01 (P = 0.31)												
Total (95% CI)		**75**		**63**	**100.0%**	**0.81 [0.54 , 1.22]**						
Total events:	27		28									
Heterogeneity: Not applicable												
Test for overall effect: Z = 1.01 (P = 0.31)												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status: new need for oxygen by mask or nasal prongs
(C) Bias due to missing outcome data: Worsening of clinical status: new need for oxygen by mask or nasal prongs
(D) Bias in measurement of the outcome: Worsening of clinical status: new need for oxygen by mask or nasal prongs
(E) Bias in selection of the reported result: Worsening of clinical status: new need for oxygen by mask or nasal prongs
(F) Overall bias: Worsening of clinical status: new need for oxygen by mask or nasal prongs

Analysis 1.8. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 8: Viral clearance

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.8.1 Viral clearance at baseline												
Wang 2020	24	131	13	65	100.0%	0.92 [0.50 , 1.68]	?	+	-	+	-	-
Subtotal (95% CI)		**131**		**65**	**100.0%**	**0.92 [0.50 , 1.68]**						
Total events:	24		13									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.28 (P = 0.78)												
1.8.2 Viral clearance at day 3												
Wang 2020	37	131	19	65	100.0%	0.97 [0.61 , 1.54]	?	+	-	+	-	-
Subtotal (95% CI)		**131**		**65**	**100.0%**	**0.97 [0.61 , 1.54]**						
Total events:	37		19									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.14 (P = 0.89)												
1.8.3 Viral clearance at day 7												
Wang 2020	66	131	32	65	100.0%	1.02 [0.76 , 1.38]	?	+	-	+	-	-
Subtotal (95% CI)		**131**		**65**	**100.0%**	**1.02 [0.76 , 1.38]**						
Total events:	66		32									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.15 (P = 0.88)												
1.8.4 Viral clearance at day 14												
Wang 2020	93	131	49	65	100.0%	0.94 [0.79 , 1.12]	?	+	-	+	-	-
Subtotal (95% CI)		**131**		**65**	**100.0%**	**0.94 [0.79 , 1.12]**						
Total events:	93		49									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.67 (P = 0.51)												

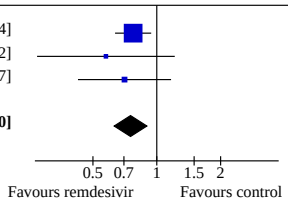


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Viral clearance
(C) Bias due to missing outcome data: Viral clearance
(D) Bias in measurement of the outcome: Viral clearance
(E) Bias in selection of the reported result: Viral clearance
(F) Overall bias: Viral clearance

Analysis 1.9. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 9: Serious adverse events

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Beigel 2020	130	532	163	516	82.0%	0.77 [0.64 , 0.94]	+ ? ? + + ?
Spinner 2020	10	193	18	200	5.6%	0.58 [0.27 , 1.22]	+ + ? + + ?
Wang 2020	28	155	20	78	12.4%	0.70 [0.43 , 1.17]	? + ? + + ?
Total (95% CI)		**880**		**794**	**100.0%**	**0.75 [0.63 , 0.90]**	
Total events:	168		201				

Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 3.15 (P = 0.002)
Test for subgroup differences: Not applicable

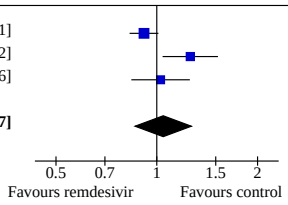


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Analysis 1.10. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 10: Adverse events, any grade

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Beigel 2020	305	532	323	516	39.4%	0.92 [0.83 , 1.01]	+ ? ? + + ?
Spinner 2020	113	193	93	200	30.8%	1.26 [1.04 , 1.52]	+ + ? ? + ?
Wang 2020	102	155	50	78	29.8%	1.03 [0.84 , 1.26]	? + ? + + ?
Total (95% CI)		**880**		**794**	**100.0%**	**1.05 [0.86 , 1.27]**	
Total events:	520		466				

Heterogeneity: Tau² = 0.02; Chi² = 8.67, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable

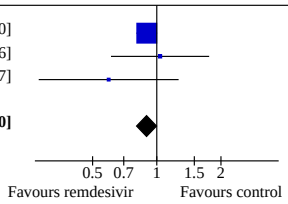


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Adverse events, any grade
(C) Bias due to missing outcome data: Adverse events, any grade
(D) Bias in measurement of the outcome: Adverse events, any grade
(E) Bias in selection of the reported result: Adverse events, any grade
(F) Overall bias: Adverse events, any grade

Analysis 1.11. Comparison 1: Remdesivir versus placebo or standard care alone, Outcome 11: Adverse events, grade 3 to 4

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Beigel 2020	273	532	295	516	93.8%	0.90 [0.80 , 1.00]	+	?	?	+	+	?
Spinner 2020	24	193	24	200	4.1%	1.04 [0.61 , 1.76]	+	+	?	+	?	?
Wang 2020	13	155	11	78	2.0%	0.59 [0.28 , 1.27]	?	+	?	+	+	?
Total (95% CI)		**880**		**794**	**100.0%**	**0.90 [0.80 , 1.00]**						
Total events:	310		330									

Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable

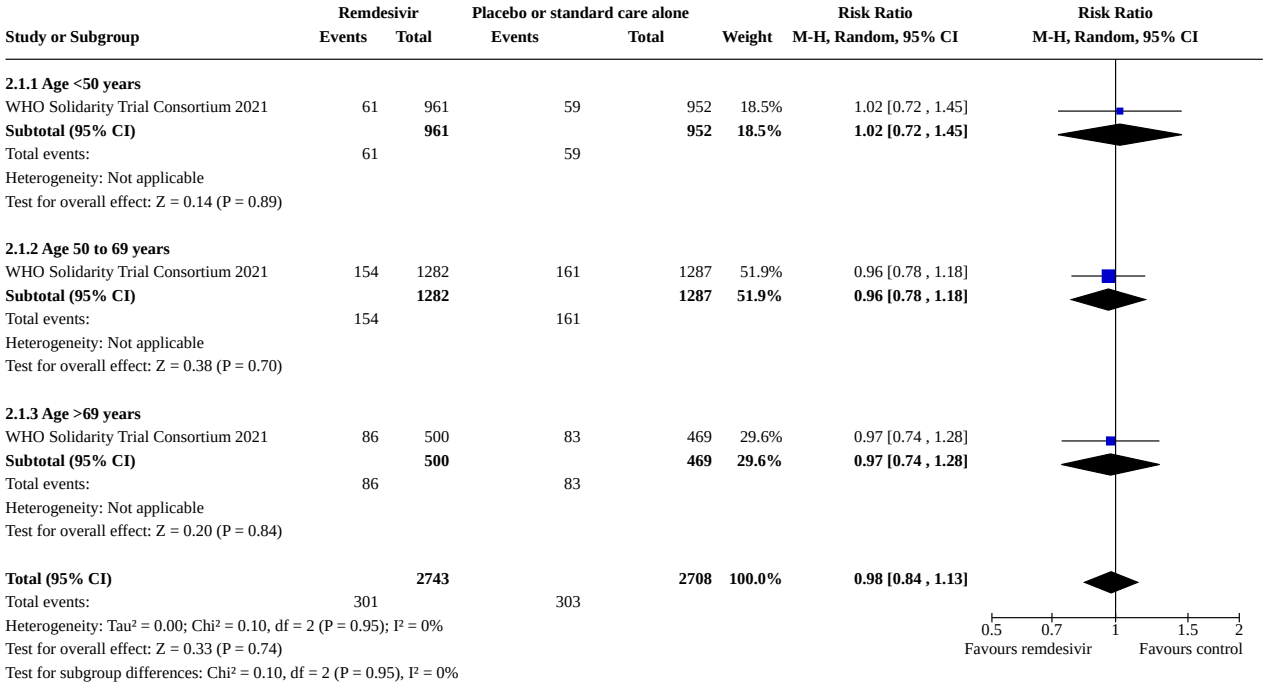


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Adverse events, grade 3 to 4
(C) Bias due to missing outcome data: Adverse events, grade 3 to 4
(D) Bias in measurement of the outcome: Adverse events, grade 3 to 4
(E) Bias in selection of the reported result: Adverse events, grade 3 to 4
(F) Overall bias: Adverse events, grade 3 to 4

Comparison 2. Subgroup analysis (age of participants): remdesivir versus placebo or standard care alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality at up to day 28	1	5451	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.13]
2.1.1 Age <50 years	1	1913	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]
2.1.2 Age 50 to 69 years	1	2569	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.78, 1.18]
2.1.3 Age >69 years	1	969	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.74, 1.28]

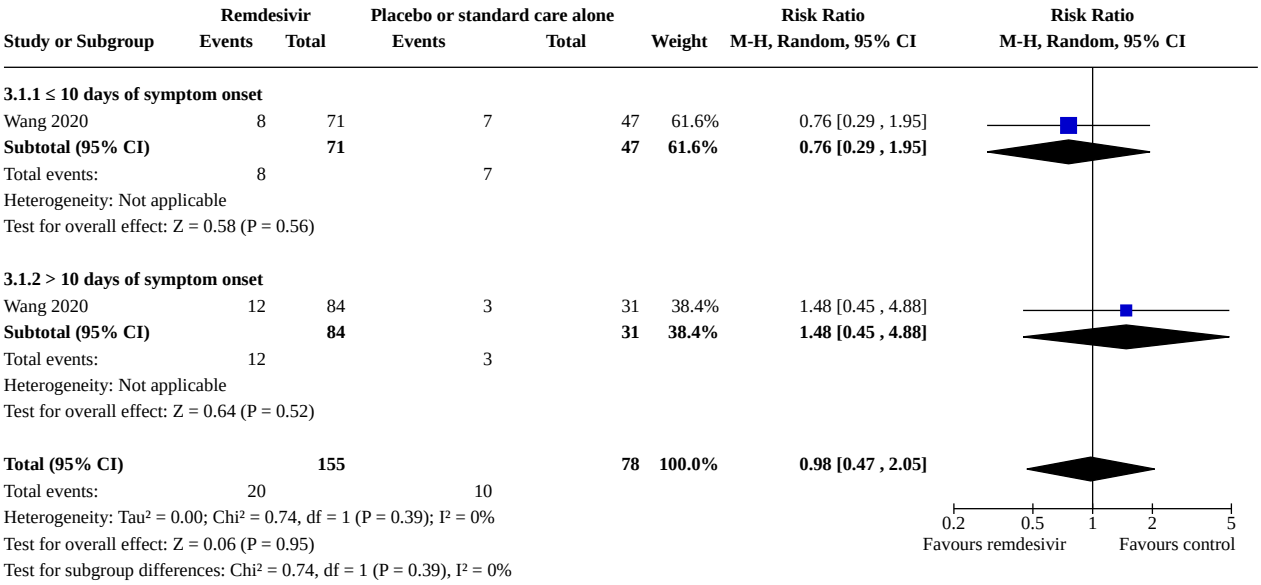
Analysis 2.1. Comparison 2: Subgroup analysis (age of participants): remdesivir versus placebo or standard care alone, Outcome 1: All-cause mortality at up to day 28



Comparison 3. Subgroup analysis (timing of first dose administration with illness onset): remdesivir versus placebo or standard care alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality at up to day 28	1	233	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.47, 2.05]
3.1.1 ≤ 10 days of symptom onset	1	118	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.29, 1.95]
3.1.2 > 10 days of symptom onset	1	115	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.45, 4.88]

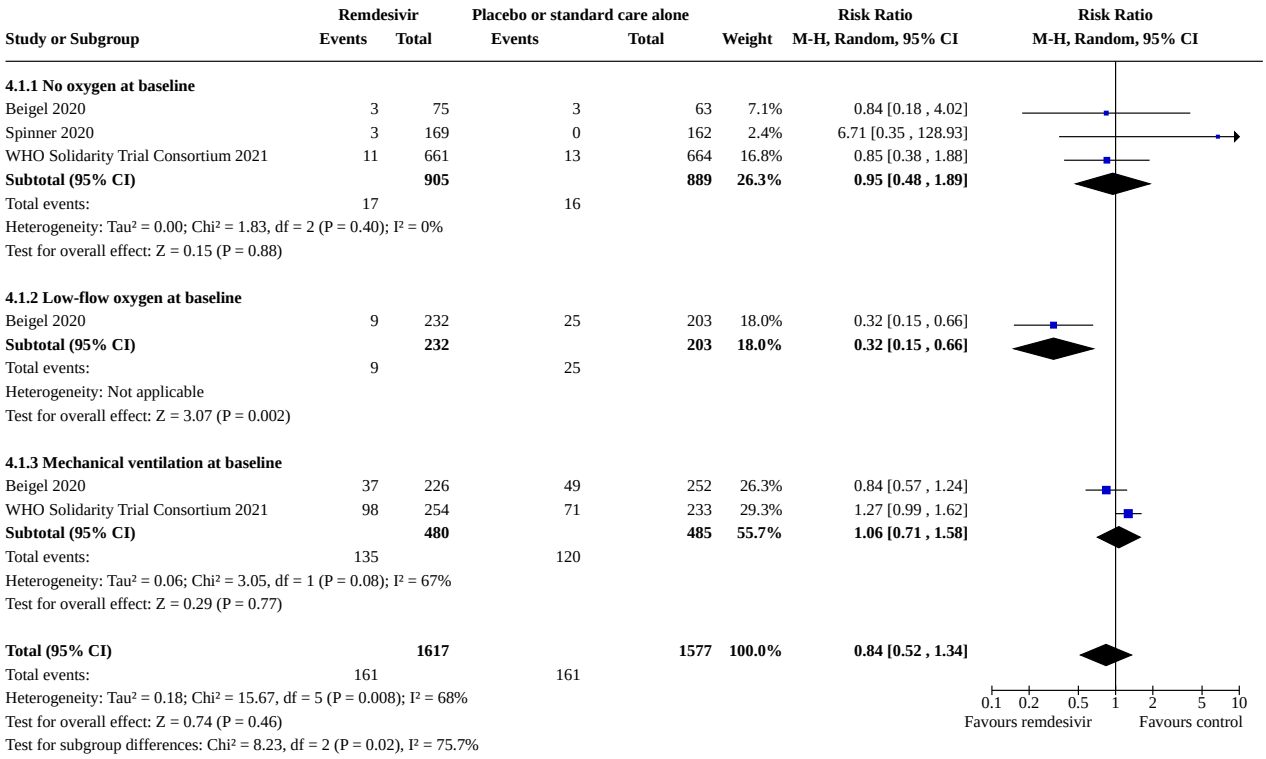
Analysis 3.1. Comparison 3: Subgroup analysis (timing of first dose administration with illness onset): remdesivir versus placebo or standard care alone, Outcome 1: All-cause mortality at up to day 28



Comparison 4. Subgroup analysis (severity of condition, no oxygen versus low-flow oxygen versus mechanical ventilation (including high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and ECMO): remdesivir versus placebo or standard care alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality at up to day 28	3	3194	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.52, 1.34]
4.1.1 No oxygen at baseline	3	1794	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.48, 1.89]
4.1.2 Low-flow oxygen at baseline	1	435	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.15, 0.66]
4.1.3 Mechanical ventilation at baseline	2	965	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.58]

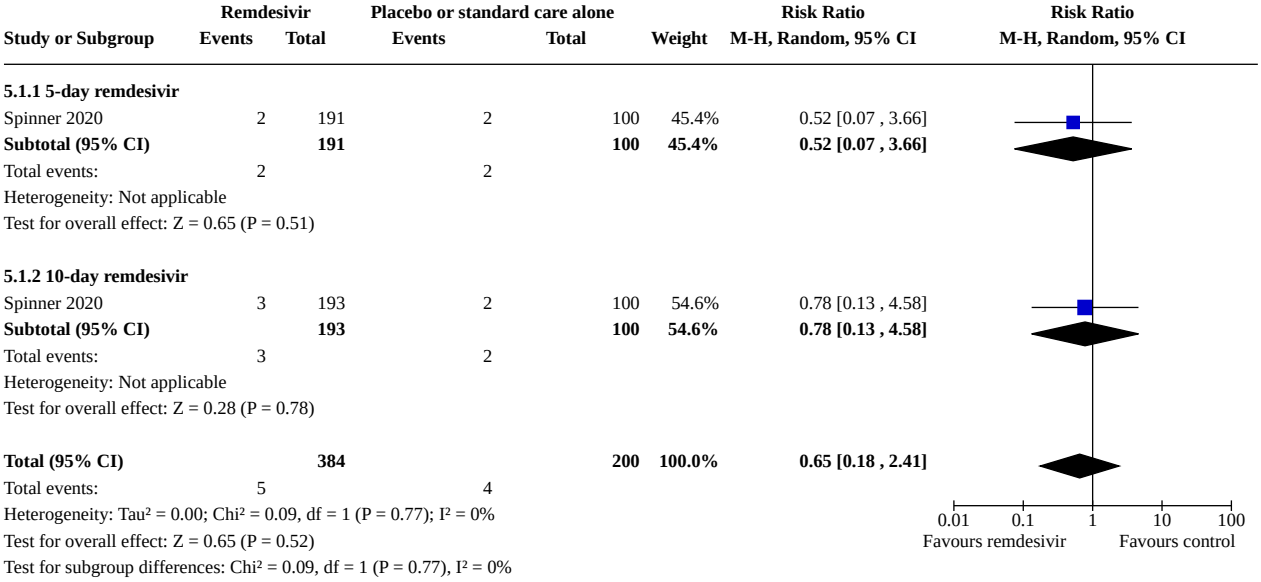
Analysis 4.1. Comparison 4: Subgroup analysis (severity of condition, no oxygen versus low-flow oxygen versus mechanical ventilation (including high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and ECMO): remdesivir versus placebo or standard care alone, Outcome 1: All-cause mortality at up to day 28



Comparison 5. Subgroup analysis (duration of remdesivir application): remdesivir versus placebo or standard care alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All-cause mortality at up to day 28	1	584	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.18, 2.41]
5.1.1 5-day remdesivir	1	291	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.07, 3.66]
5.1.2 10-day remdesivir	1	293	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.13, 4.58]

Analysis 5.1. Comparison 5: Subgroup analysis (duration of remdesivir application): remdesivir versus placebo or standard care alone, Outcome 1: All-cause mortality at up to day 28



ADDITIONAL TABLES

Table 1. Glossary

Phrase/Word	Meaning/Description
Acute respiratory distress syndrome (ARDS)	ARDS is characterised by a massive response of the respiratory system to a wide variety of external and internal noxious stimuli. There is a disturbance of oxygen uptake and an acute onset. ARDS is the common end route of a wide variety of diseases leading to a severe systemic inflammatory response. The condition should be distinguished from disturbances of respiration caused by cardiac diseases.
Adverse event	An adverse event in the context of clinical trials is an unwanted medical occurrence in patients receiving a pharmacological or non-pharmacological treatment, or both. An adverse event may not necessarily be considered to be related to the treatment.
Antimicrobials	Drugs used to treat diseases caused by micro-organisms (bacteria, fungi, viruses, parasites).
Antiviral (medicine)	An agent that is directed against viruses
Bias	(Unconscious) distortion and misinterpretation of research results, especially those obtained experimentally. The most important sources for bias are as follows. • Selection bias: people are more likely to be included in the study if they have a certain characteristic (age, gender, ethnicity, social class, etc.). • Information bias: the data collected as part of the study is subject to error. • Publication bias: studies that show statistically significant results are published preferentially. • Confounding: the result of a study is distorted by interference.
Controlled non-randomised study	A study in which the effects of a pharmacological or non-pharmacological measure, or both, are compared between different groups of participants. The term 'controlled' means that the measure under investigation (intervention, verum) is compared with another measure (placebo or another intervention). The group of participants receiving the intervention under study is known as the intervention group. The group of participants who do not receive the intervention is known as

Table 1. Glossary *(Continued)*

	the control group. A controlled non-randomised study is easier to conduct than a randomised controlled trial, but has much less power (see bias).
Convalescent plasma	Blood plasma from patients who have had a disease (e.g. COVID-19). Transfer of convalescent plasma to naive patients (patients who do not have antibodies themselves) leads to an increase in the immune defence of the receiving patient because convalescent plasma contains antibodies.
Corticosteroids	Hormones that are mainly produced in the adrenal cortex. Corticosteroids influence many biological processes in the organism, and are in particular closely linked to the immune system. Important naturally occurring representatives are cortisone and cortisol. Examples of synthetically produced corticosteroids are dexamethasone and budesonide.
Dichotomous	Dichotomy describes a system that can have exactly two mutually exclusive states. Example: either one has a certain disease (state A), or one does not have this disease (state B). The co-occurrence of state A and state B is impossible.
Ebola	Ebola is a viral disease that is often severe. The Ebola virus belongs to the *Filoviridae* (from Latin 'filum' = filamentous). There are at least six different species of the virus. Ebola virus was previously called haemorrhagic fever because it is accompanied by high fever and severe internal and external bleeding.
Heterogeneous	Heterogeneity can be translated as 'non-uniformity'. It is the opposite of homogeneity. In the context of meta-analyses, heterogeneity is a measure of the comparability of clinical trials. For example, studies that examine different populations (e.g. children versus adults) have limited comparability and can lead to misleading conclusions when the data from such studies are pooled in a meta-analysis.
Hydroxychloroquine	A drug related to chloroquine, which is used mainly for the treatment of rheumatoid arthritis, lupus erythematosus, and the prevention of malaria
Immunocompromised status	Immunocompromised are people who have a congenital or acquired disorder of the immune response. Examples of acquired disorders include infection with HIV. Long-term treatment with certain drugs (e.g. corticosteroids) can also lead to disorders/weakening of the immune response.
Interventions	The term 'intervention' in the context of clinical trials refers to the measure whose effect (superiority, inferiority, non-inferiority) on a specific condition is to be assessed in comparison to other measures. An intervention need not always consist of the administration of a specific drug (so-called non-pharmacological interventions).
Mechanical ventilation	Mechanical ventilation is the term used to describe a procedure in which oxygen is supplied to the patient with the aid of ventilators or other devices. This measure is very restrictive and not without risk, and is therefore used only if the patient can no longer take in enough oxygen through his or her natural breathing (spontaneous respiration). In **this review**, the following procedures are subsumed under the term 'mechanical ventilation'. • High-flow nasal cannula: oxygen is applied to the patient through the nose at a high flow rate. In addition to the oxygen, the patient can still breathe room air. • Non-invasive mechanical ventilation: the patient is assisted in breathing by applying pressure during exhalation and/or inhalation, for example via a tight-fitting mask or a ventilation helmet. As a rule, the patient is awake during this process. Sensitive guidance of the patient is particularly important. • Invasive mechanical ventilation: the patient is intubated (a breathing tube is inserted into the trachea) and ventilated by a machine.
Middle East respiratory syndrome (MERS)	MERS is a respiratory disease caused by a coronavirus (MERS-CoV). Most cases of the disease are asymptomatic. Diarrhoea is a common accompanying symptom. In severe cases, pneumonia develops.

Table 1. Glossary *(Continued)*

Monoclonal antibody (MAB)	Antibodies in general are produced by the organism (specifically the immune system) when it is exposed to an antigen (for example, pathogenic microorganisms and viruses). By reacting with specific parts of the antigen, the antibody can render it harmless. So-called monoclonal antibodies are produced by infecting mice with an antigen, for example. The immune system (especially the B cells) of the infected mouse then produces antibodies that are specifically active against the antigen. These cells accumulate in the spleen of the infected mouse. These cells are then isolated from the animal's spleen in a complicated process and multiplied in vitro (i.e. in the test tube). The resulting monoclonal antibodies are all derived from genetically identical cells and are directed against a specific antigen. Monoclonal antibodies are administered in medicine when the patient does not produce any antibodies or produces too few of his or her own. In addition, these specific antibodies also enable the identification of antigens in the detection of various diseases.
Nasal prongs	Nasal prongs, or nasal cannula, is a device used to deliver low-flow oxygen to the nose through a small plastic tube.
Observational study	Data collection in a specific population under a specific research question. The essential characteristic of an observational study is that no intervention/experiment is carried out.
Placebo	A placebo is a dummy drug that does not contain a pharmacologically active substance.
Randomised controlled trial	A randomised controlled trial is the best way to obtain conclusions regarding the efficacy and effectiveness of a pharmacological or non-pharmacological intervention, or both. The term 'controlled' means that the measure under investigation (intervention, verum) is compared with another measure (placebo or another intervention). The term 'randomised' means that the participants in the study are randomly assigned to one of two or more prespecified treatment groups. The group of participants receiving the intervention under study is known as the intervention group. The group of participants who do not receive the intervention is known as the control group.
Severe acute respiratory syndrome (SARS)	A disease caused by SARS-CoV, which, similar to COVID-19, results in fever and muscle pain in combination with other flu-like signs. In severe cases, atypical pneumonia may occur.
Systematic review	Scientific process of critical judgement of the data available with regard to a specific question. A 'systematic' approach is taken. This includes: • formulation of a research question; • systematic and comprehensive search for data (studies); • clearly defined criteria that the identified studies must fulfil in order to be included in the evaluation; • repeatable and uniform guidelines for data analysis. A systematic review can include a meta-analysis, but this is not required. The aim of a systematic review is to answer the defined research question, or, if this is not possible, to identify gaps in the scientific coverage of the research question.

Table 2. Characteristics of ongoing studies

Study ID	Comparison	Expected completion date
NCT04252664	Remdesivir compared to placebo	Recruiting completed, no publication available yet
NCT04596839	Remdesivir compared to standard care	Recruiting

Table 3. Overview of included studies

	Beigel 2020 [a]	Spinner 2020	Wang 2020	WHO Solidarity Trial Consortium 2021	Mahajan 2021
	(By date of publication)				
Setting	• Inpatient • Multinational	• Inpatient • Multinational	• Inpatient • China	• Inpatient • Multinational	• Inpatient • India
Design	• Randomised • Double-blind • Placebo-controlled	• Randomised • Open-label • Controlled	• Randomised • Double-blind • Placebo-controlled	• Randomised • Open-label • Controlled	• Randomised • Open-label • Controlled
Study protocol	Reported	Reported	Reported	Reported	Not reported
Statistical analysis plan	Reported	Reported	Reported	Reported	Not reported
Intervention (remdesivir) **(duration of application (days))**	10	5 or 10	10	10	5
Control	SoC	Placebo + SoC	Placebo + SoC	SoC	SoC
Allocated participants (n)	1062	596	236	5475	82
Number of participants **per trial arm (allocated/evaluated)**	Intervention: 541/541 Placebo + SoC: 521/521	5-day intervention: 199/191 10-day intervention: 197/193 SoC: 200/200	Intervention: 158/158 Placebo + SoC: 78/78	Intervention: 2750/2743 SoC: 2725/2708	Intervention: 41/34 SoC: 41/36
	Clinical characteristics at baseline (all participants were hospitalised; ordered according to WHO Progression Scale, see Table 4) (n/N (%))				
No need for oxygen or medical care **(not part of WHO 2020d)**	NA	5-day intervention: 0/191 (83.8) 10-day intervention: 6/193 (3.2) SoC: 2/200 (1.0)	NA	NA	NA
WHO 3	NA	NA	NA	NA	NA
WHO 4	Intervention: 75/541 (13.9)	5-day intervention: 160/191 (83.8)	Intervention: 0/158 (0)	Intervention: 661/2743 (24.1)	NA

Table 3. Overview of included studies *(Continued)*

	Placebo: 63/521 (12.1)	10-day intervention: 163/193 (84.5) SoC: 160/200 (80.0)	Placebo + SoC: 3/78 (3.8)	SoC: 664/2708 (24.5)	
WHO 5	Intervention: 232/541 (42.9) Placebo: 203/521 (39.0)	5-day intervention: 29/191 (15.2) 10-day intervention: 23/193 SoC: 36/200 (18.0)	Intervention: 129/158 (81.6) Placebo + SoC: 65/78 (83.3)	Intervention: 1828/2743 (66.4) SoC: 1811/2708 (66.9)	Intervention: 27/34 (79.4) SoC: 26/36 (72.2)
WHO 6	Intervention: 95/541 (17.6) Placebo: 98/521 (18.8)	5-day intervention: 2/191 (1.0) 10-day intervention: 1/193 (0.5) SoC: 2/200 (1.0)	Intervention: 28/158 (17.2) Placebo + SoC: 9/78 (11.5)	NA	Intervention: 7/34 (20.6) SoC: 10/36 (27.8)
WHO 7 **WHO 8** **WHO 9**	Intervention: 131/541 (24.2) Placebo: 154/521 (29.6)	NA	Intervention: 0/158 (0) Placebo + SoC: 1/78 (1.3)	Intervention: 254/2743 (9.3) SoC: 233/2708 (8.6)	NA
WHO 10	NA	NA	Intervention: 1/158 (0.6) Placebo + SoC: 0/78 (0)	NA	NA
	Demographics				
Age (years)	**Mean (SD)** Intervention: 58.6 (14.6) Placebo: 59.2 (15.4)	**Median (IQR)** 5-day intervention: 58 (48 to 66) 10-day intervention: 56 (45 to 66) SoC: 57 (45 to 66)	**Median (IQR)** Intervention: 66 (57 to 73) Placebo: 64 (53 to 70)	**n/Total** **< 50** Intervention: 961/2743 SoC: 952/2708 **50 to 69** Intervention: 1282/2743 SoC: 1287/2708 **≧ 70** Intervention: 500/2743 SoC: 268/2708	**Mean (SD)** Intervention: 58.09 (12.1) SoC: 57.41 (14.1)
Gender (male (n(%)))	Intervention: 352/541 (65.1) Placebo: 332/521 (63.7)	5-day intervention: 114/191 (59.7) 10-day intervention: 118/193 (61.1)	Intervention: 89/158 (56.3) Placebo: 51/78 (65.4)	Intervention: 1706/2743 (62.2) SoC: 1725/2708 (63.7)	Intervention: 21/34 (61.8) SoC: 27/36 (75.0)

Table 3. Overview of included studies *(Continued)*

		SoC: 125/200 (62.5)			
	Comorbidities at baseline (n (%))				
Diabetes	Intervention: 164 (30.8) Placebo: 158 (30.4)	5-day intervention: 71 (37) 10-day intervention: 85 (44) SoC: 76/200 (38)	Intervention: 40 (25) Placebo: 16 (21)	Intervention: 707 (26) SoC: 666 (25)	Intervention: 21 (62) SoC: 21 (58)
Hypertension	Intervention: 269 (50.6) Placebo: 264 (50.9)	5-day intervention: 82 (43) 10-day intervention: 85 (44) SoC: 81 (41)	Intervention: 73 (46) Placebo: 30 (38)	Not reported	Intervention: 15 (44) SoC: 17 (47)
CAD	Not reported	5-day intervention: 111 (58) 10-day intervention: 111 (58) SoC: 107 (54)	Intervention: 15 (9) Placebo: 2 (3)	Not reported	Intervention: 4 (12) SoC: 5 (14)
COPD	Not reported	Not reported	Not reported	Intervention: 151 (6) SoC: 145 (5)	Not reported
Asthma	Not reported	5-day intervention: 22 (12) 10-day intervention: 31 (16) SoC: 28 (14)	Not reported	Intervention: 139 (5) SoC: 139 (5)	Intervention: 1 (3) SoC: 0 (0)
Obesity	Intervention: 242 (46) Placebo: 234 (45)	BMI (median (IQR)) 5-day intervention: 27 (24 to 30) 10-day intervention: 28 (25 to 32) SoC: 27 (24 to 31)	Not reported	Not reported	Not reported
CLD	Not reported	Not reported	Not reported	Intervention: 36 (1) SoC: 41 (2)	Not reported
CKD	Not reported	Not reported	Not reported	Not reported	Intervention: 2 (6) SoC: 1 (3)
Other	Not reported	Not reported	Not reported	**Unspecified heart disease** Intervention: 571 (21) SoC: 567 (21)	**Hyperlipidaemia** Intervention: 4 (12) SoC: 3 (8) **Hypothyroidism**

Table 3. Overview of included studies *(Continued)*

					Intervention: 4 (12) SoC: 3 (8)
	Concomitant medications (n(%))				
Corticosteroids	Intervention: 115 (21.6) Placebo: 126 (24.4)	5-day intervention: 33 (17) 10-day intervention: 29 (15) SoC: 38 (19)	Intervention: 60 (38) Placebo: 31 (40)	Intervention: 1310 (48) SoC: 1288 (48)	Not reported
HCQ/CQ	Intervention: 184 (35) Placebo: 189 (37)	5-day intervention: 16 (8) 5-day intervention: 22 (11) SoC: 89 (45)	Not reported	Not reported	Not reported
Lopinavir-ritonavir	Not reported	5-day intervention: 10 (5) 10-day intervention: 11 (6) SoC: 43 (22)	Intervention: 27 (17) Placebo: 31 (40)	Not reported	Not reported
MAB (interleukin 6)	Intervention: 23 (4.3) Placebo: 26 (5.0)	5-day intervention: 1 (1) 10-day intervention: 1 (1) SoC: 10 (5)	Not reported	Intervention: 133 (5) SoC: 143 (5)	Not reported
Azithromycin	Not reported	5-day intervention: 35 (18) 10-day intervention: 41 (21) SoC: 62 (31)	Not reported	Not reported	Not reported
Other	**Antibiotics** Intervention: 420 (79) Placebo: 443 (86) **Vasopressors** Intervention: 147 (28) Placebo: 195 (38) **Other anti-inflammatory** **medications** Intervention: 42 (8) Placebo: 37 (7) **Other biologic therapies** Intervention: 21 (4) Placebo: 13 (3)	Not reported	**Antibiotics** Intervention: 121 (77) Placebo: 63 (81) **Interferon alfa-2b** Intervention: 29 (18) Placebo: 15 (19)	**Convalescent plasma** Intervention: 52 (2) SoC: 58 (2) **Interferon** Intervention: 3 (0.1) SoC: 25 (1) **Antiviral other than RDV** Intervention: 65 (2) SoC: 152 (6)	Not reported

Table 3. Overview of included studies *(Continued)*

Other putative SARS-CoV-2 medications	
Intervention: 8 (2)	
Placebo: 14 (3)	
Other antiviral medications	
Intervention: 10 (2)	
Placebo: 8 (2)	

[a]Missing data at baseline (n/N): intervention: 8/541, placebo: 3/521.
BMI = body mass index
CAD = coronary artery disease
CKD = chronic kidney disease
CLD = chronic liver disease
COPD = chronic obstructive pulmonary disease
HCQ/CQ = hydroxychlorquine/chloroquine
IQR = interquartile range
MAB = monoclonal antibodies
NA = not available/not applicable
RDV = remdesivir
SD = standard deviation
SoC = standard of care
WHO = World Health Organization

Table 4. Conversion between ordinal clinical progression scales used by included studies and WHO Clinical Progression Scale

	WHO 2020d	Description	Beigel 2020	Spinner 2020	Wang 2020	WHO Solidarity Trial Consortium 2021	Mahajan 2021	
							Day 1 to day 12	Day 12 to day 24
Ambulatory: mild disease	1	**Asymptomatic Viral RNA detected**	1	7	1	NA	NA	1
	2	**Symptomatic Independent**				NA	NA	
	3	**Symptomatic Assistance needed**	2			NA	NA	
Hospitalised: moderate disease	NA	**No oxygen or medical care**	3	6	NA	No supplemental oxygen	NA	NA
	4	**No oxygen therapy**	4	5	2		3	2
	5	**Oxygen by mask or nasal prongs**	5	4	3	Supplemental oxygen	1	3
Hospitalised: severe disease	6	**Oxygen by NIV or high-flow**	6	3	4	NA	2	4
	7	**Intubation and IMV $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$**	7	2	5	IMV	4	5
	8	**IMV and $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) OR vasopressors**						
	9	**IMV and**						

Table 4. Conversion between ordinal clinical progression scales used by included studies and WHO Clinical Progression Scale *(Continued)*

		pO_2/FiO_2 < 150 and vasopressors, dialysis, or ECMO					
10	**Dead**	8	1	6	NA	NA	NA

ECMO = extracorporeal membrane oxygenation
FiO_2 = fraction of inspired oxygen
IMV = invasive mechanical ventilation
NA = not applicable
NIV = non-invasive mechanical ventilation
pO_2 = partial pressure of oxygen
RNA = ribonucleic acid
SpO_2 = oxygen saturation

Table 5. Narrative summary of outcomes of included studies

Beigel 2020

Study outcomes (time point, definition)	Reported outcome data (R: remdesivir group, C: control group)
All-cause mortality 1. At up to day 15 2. At up to day 29 3. Time-to-event	1.**Mortality at up to day 15, n/N (%); HR (95% CI)** • R: 35/541 (6.5) versus C: 61/521 (11.7); 0.55 (0.36 to 0.83) 2. **Mortality at up to day 29**: included in analysis (Analysis 1.1). 3. **Mortality, time-to-event**: included in analysis (Analysis 1.3).
Clinical status with mean change in ordinal scale compared to baseline • At day 15 • At day 29 8-category ordinal scale: 1. Not hospitalised and no limitations of activities 2. Not hospitalised, with limitation of activities, home oxygen requirement, or both 3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection control or other non-medical reasons) 4. Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or to other medical conditions) 5. Hospitalised, requiring any supplemental oxygen 6. Hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices 7. Hospitalised, receiving invasive mechanical ventilation or ECMO 8. Death	**Clinical status at day 15, n/N (%)** 1. R: 157/541(29.0) versus C: 115/521 (22.1) 2. R: 117/541 (21.6) versus C: 102/521 (19.6) 3. R: 14/541 (2.6) versus C: 8/521(1.5) 4. R: 38/541 (7.0) versus C: 33/521 (6.3) 5. R: 58/541 (10.7) versus C: 60/521 (11.5) 6. R: 28/541 (5.2) versus C: 24/521 (4.6) 7. R: 95/541 (17.6) versus C: 121/521 (23.2) 8. R: 34/541 (6.3) versus C: 58/521 (11.1) **Mean ordinal scale (SD) at day 15; mean change from baseline scale (SD) at day 15: R: 3.7 (2.5); −1.9 (2.1) versus C: 4.3 (2.6); −1.4 (2.3)** 1. **Clinical status at day 29, n/N (%)** 2. R: 247/541 (46.0) versus C: 190/521 (36.0) 3. R: 107/541 (20.0) versus C: 100/521 (19.0) 4. R: 3/541 (1.0) versus C: 4/521 (1.0) 5. R: 16/541 (3.0) versus C: 18/521 (3.0) 6. R: 23/541 (4.0) versus C: 22/521 (4.0) 7. R: 3/541 (1.0) versus C: 10/521 (2.0) 8. R: 30/541 (6.0) versus C: 45/521 (9.0) 9. R: 58/541 (11.0) versus C: 76/521 (15.0) **Mean ordinal scale (SD) at day 29; mean change from baseline scale (SD) at day 29: R: 2.8 (2.5); −2.79 (2.3) versus C: 3.4 (2.7); −2.3 (2.6)**
Clinical improvement • Time to improvement of 1 category and of 2 categories from the baseline ordinal score • Liberation from respiratory support: number of participants changing from category 5 to ≤ 4 (low-flow oxygen), number of participants changing from category 6 to ≤ 5 (NIV or high-flow oxygen), number of participants changing from category 7 to ≤ 6 (IMV or ECMO) at up to day 15 • Duration to liberation from respiratory support: number of days with supplemental oxygen, with non-invasive ventilation or high-flow oxygen, and with invasive ventilation or ECMO up to day 29, if these were being used at baseline	• **Median time to clinical improvement, days (95% CI)** a. Improvement of 1 category on ordinal scale * R: 7.0 (6.0 to 8.0) versus C: 9.0 (8.0 to 11.0) * Rate ratio: 1.23 (95% CI 1.08 to 1.41) b. Improvement of 2 categories on ordinal scale * R: 11.0 (10.0 to 13.0) versus C: 14.0 (13.0 to 15.0) * Rate ratio: 1.29 (95% CI 1.12 to 1.48) • **Liberation from respiratory support at up to day 15, n/N (%)** a. Oxygen: R: 183/232 (78.9) versus C: 137/203 (67.5) b. NIV or high-flow oxygen: R: 54/95 (56.8) versus C: 51/98 (52) c. IMV or ECMO: R: 60/131 (45.8) versus C: 59/154 (38.3) • **Duration to liberation from respiratory support, median days (IQR); difference (95% CI)** a. Oxygen: R: 13 (5 to 28) versus C: 21 (8 to 28); −8.0 (−11.8 to −4.2) b. NIV or high-flow oxygen: R: 6 (3 to 18) versus C: 6 (3 to 16); 0 (−2.6 to 2.6) c. IMV or ECMO: R: 17 (9 to 28) versus C: 20 (8 to 28); −3.0 (−9.3 to 3.3)

Table 5. Narrative summary of outcomes of included studies *(Continued)*

• Odds ratio for improvement at day 15
• Time to recovery, defined as the first day, during the 28 days after enrolment, on which a patient met the criteria for discharge (no need for supplemental oxygen or inpatient medical care)
• Time to discharge or National Early Warning Score of 2 or less (maintained for 24 hours), whichever occurred first
	• **Odds ratio for improvement at day 15**
	  * 1.5 (95% CI 1.2 to 1.9)
	• **Time to recovery, days (IQR)**
	  a. R: 10 (9 to 11) days versus C: 15 (13 to 18) days
	• **Time to discharge or National Early Warning Score ≤ 2 for 24 h, days (IQR)**
	  * R: 8 (7 to 9) versus C: 12 (10 to 15)
	  * Rate ratio: 1.27 (95% CI 1.10 to 1.46)

Clinical worsening Incidence of new oxygen use, of non-invasive ventilation or high-flow oxygen, and of invasive ventilation or ECMO	**Initiation of respiratory support:** Included in analysis (Analysis 1.5; Analysis 1.6; Analysis 1.7).
Duration of hospitalisation up to day 29. • Patients rehospitalised	**Initial length of hospital stay, median days (IQR)** • R: 12 (6 to 28) versus C: 17 (18 to 28) **Patients rehospitalised, per cent (95% CI); difference (95% CI)** • R: 5 (3 to 7) versus C: 3 (2 to 5); 2 percentage points (0 to 4)
Safety outcomes • Adverse events, any grade * Adverse events grade 3 to 4 • Serious adverse events	**Safety outcomes:** included in analysis (Analysis 1.9; Analysis 1.10; Analysis 1.11).
Mahajan 2021	
Study outcomes (time point, definition)	**Reported outcome data**
All-cause mortality • From day 12 to 24	**Death from day 12 to day 24, n/N (%)** • R: 5/34 (14.7) versus C: 3/36 (8.3)
Clinical status from day 12 to 24 6-point ordinal scale 1. Did not require hospitalisation 2. Hospitalised, but did not require supplemental oxygen 3. Hospitalised, required supplemental oxygen 4. Required `high-flow` oxygen or `non-invasive` ventilation 5. Required or received mechanical ventilation 6. Death	**Clinical status from day 12 to 24, n/N (%)** 1. R: 2/34 (5.9) versus C: 3/36 (8.3) 2. R: 0 versus C: 0 3. R: 4/34 (11.8) versus C: 6/36 (16.7) 4. R: 19/34 (55.9) versus C: 22/36 (61.1) 5. R: 4/34 (11.8) versus C: 2/36 (5.6) 6. R: 5/34 (14.7) versus C: 3/36 (8.3)
Duration of hospitalisation	**Admission days, mean (SD)** • R: 11.55 (4.3) versus C: 12.38 (5.2)

Table 5. Narrative summary of outcomes of included studies *(Continued)*

Safety outcomes 1. Nausea and vomiting 2. Increase in liver enzymes (AST levels) 3. Increase in liver enzymes (ALT levels) 4. Increase in creatinine levels	1. Nausea and vomiting, n at baseline versus n after treatment • R: 7 versus 3; C: 9 versus 2 2. Increase in liver enzymes (AST levels), at baseline versus after treatment • R: 37.09 ± 11.4 versus 38.06 ± 10.9; C: 38.03 ± 12.2 versus 39.01 ± 11.2 3. Increase in liver enzymes (ALT levels), at baseline versus after treatment • R: 38.94 ± 13.4 versus 39.01 ± 12.3; C: 35.19 ± 13.6 versus 36.21 ± 13.2 4. Increase in creatinine levels, at baseline versus after treatment • R: 0.98 ± 0.13 versus 1.12 ± 0.15; C: 1.01 + 0.15 versus 1.56 ± 0.67

Spinner 2020

Study outcomes (time point, definition)	Reported outcome data
All-cause mortality 1. At up to day 11 2. At up to day 28 3. Kaplan-Meier estimates at day 28	1. **Mortality at up to day 11, n/N (%)** • 10-day R: 2/193 (1) versus 5-day R: 0/191 (0) versus C: 4/200 (2) 2. **Mortality at up to day 28, n/N (%):** included in analysis (Analysis 1.1) 3. **Kaplan-Meier estimates of all-cause mortality at day 28, % (95% CI)** • 10-day R: 2 (0.0 to 3.6) versus 5-day R: 1 (0.0 to 2.6) versus C: 2 (0.1 to 4.1)
Clinical status at day 11 with difference in clinical status distribution and days 14, 28 7-point ordinal scale: 1. Death 2. Hospitalised, requiring invasive mechanical ventilation or ECMO 3. Hospitalised, requiring non-invasive ventilation or high-flow oxygen 4. Hospitalised, requiring low-flow supplemental oxygen 5. Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care 6. Hospitalised, not requiring supplemental oxygen or medical care 7. Not hospitalised	**Clinical status at day 11, n/N (%)** 1. 10-day R: 2/193 (1) versus 5-day R: 0/191 (0) versus C: 4/200 (2) 2. 10-day R: 1/193 (1) versus 5-day R: 0/191 (0) versus C: 4/200 (2) 3. 10-day R: 0/193 (0) versus 5-day R: 5/191 (3) versus C: 7/200 (4) 4. 10-day R: 12/193 (6) versus 5-day R: 7/191 (4) versus C: 11/200 (6) 5. 10-day R: 44/193 (23) versus 5-day R: 38/191 (20) versus C: 46/200 (23) 6. 10-day R: 9/193 (5) versus 5-day R: 7/191 (4) versus C: 8/200 (4) 7. 10-day R: 125/193 (65) versus 5-day R: 134/191 (70) versus C: 120/200 (60) • **Difference in clinical status distribution versus standard care, OR (95% CI)** * 10-day R: not reported; 5-day R: 1.65 (1.09 to 2.48) **Clinical status at day 14, n/N (%)** 1. 10-day R: 2/193 (1) versus 5-day R: 1/191 (1) versus C: 4/200 (2) 2. 10-day R: 1/193 (1) versus 5-day R: 0/191 (0) versus C: 5/200 (3) 3. 10-day R: 0/193 (0) versus 5-day R: 4/191 (2) versus C: 4/200 (2) 4. 10-day R: 4/193 (2) versus 5-day R: 5/191 (3) versus C: 8/200 (4) 5. 10-day R: 31/193 (16) versus 5-day R: 28/191 (15) versus C: 34/200 (17) 6. 10-day R: 9/193 (5) versus 5-day R: 7/191 (4) versus C: 11/200 (6) 7. 10-day R: 146/193 (76) versus 5-day R: 146/191 (76) versus C: 134/200 (67) **Clinical status at day 28, n/N (%)** 1. 10-day R: 3/193 (2) versus 5-day R: 2/191 (1) versus C: 4/200 (2) 2. 10-day R: 1/193 (1) versus 5-day R: 0/191 (0) versus C: 4/200 (2) 3. 10-day R: 1/193 (1) versus 5-day R: 1/191 (1) versus C: 0/200 (0) 4. 10-day R: 0/193 (0) versus 5-day R: 4/191 (2) versus C: 5/200 (3) 5. 10-day R: 10/193 (5) versus 5-day R: 9/191 (5) versus C: 17/200 (9) 6. 10-day R: 4/193 (2) versus 5-day R: 5/191 (3) versus C: 4/200 (2) 7. 10-day R: 174/193 (90) versus 5-day R: 170/191 (89) versus C: 166/200 (83)

Table 5. Narrative summary of outcomes of included studies *(Continued)*

Clinical improvement 1. Clinical improvement: at least 2 points from baseline on the 7-point ordinal scale at day 5, 7, 11, 14, 28 2. Difference in clinical improvement compared to standard care at day 11 3. Time to clinical improvement: ≥ 1 point improvement from baseline on the 7-point ordinal scale 4. Time to clinical improvement: ≥ 2 points improvement from baseline on the 7-point ordinal scale 5. Recovery: improvement from a baseline score of 2 to 5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7 at day 5, 7, 11, 14, 28 6. Difference in recovery compared to standard care at day 11 7. Time to recovery 8. Time to modified recovery: improvement from a baseline score of 2 to 4 to a score of 5 to 7, improvement from a baseline score of 5 to a score of 6 to 7, or improvement from a baseline score of 6 to a score of 7 9. Time to discontinuation of any oxygen support	1. **Clinical improvement, n/N (%)** • Day 5: 10-day R: 72/193 (37) versus 5-day R: 61/191 (32) versus C: 66/200 (33) • Day 7: 10-day R: 92/193 (48) versus 5-day R: 106/191 (56) versus C: 94/200 (47) • Day 11: 10-day R: 126/193 (65) versus 5-day R: 134/191 (70) versus C: 121/200 (61) • Day 14: 10-day R: 148/193 (77) versus 5-day R: 146/191 (76) versus C: 135/200 (68) • Day 28: 10-day R: 174/193 (90) versus 5-day R: 171/191 (90) versus C: 166/200 (83) 2. **Difference in clinical improvement at day 11, % (95% CI)** • 10-day R: 4.8 (−5.0 to 14.4) • 5-day R: 9.7 (0.1 to 19.1) 3. **Time to clinical improvement ≥ 1; median (25% to 75%), HR (95% CI)** • 10-day R: 7 (4 to 12); HR 1.10 (0.90 to 1.36) • 5-day R: 6 (4 to 9); HR 1.19 (0.97 to 1.47) • C: 7 (4 to 14) 4. **Time to clinical improvement ≥ 2 points; median (25% to 75%), HR (95% CI)** • 10-day R: 8 (4 to 14), HR 1.16 (0.93 to 1.43) • 5-day R: 6 (5 to 14), HR 1.15 (CI 0.93 to 1.42) 5. **Recovery, n/N (%)** • Day 5: 10-day R: 74/193 (38) versus 5-day R: 67/191 (35) versus C: 71/200 (36) • Day 7: 10-day R: 94/193 (49) versus 5-day R: 114/191 (60) versus C: 101/200 (51) • Day 11: 10-day R: 132/193 (68) versus 5-day R: 141/191 (74) versus C: 128/200 (64) • Day 14: 10-day R: 153/193 (79) versus 5-day R: 153/191 (80) versus C: 145/200 (73) • Day 28: 10-day R: 178/193 (92) versus 5-day R: 175/191 (92) versus C: 170/200 (85) 6. **Difference in recovery at day 11, % (95% CI)** • 10-day R: 4.4 (−5.0 to 13.8) • 5-day R: 9.8 (0.3 to 19.0) 7. **Time to recovery; median (25% to 75%), HR (95% CI)** • 10-day R: 8 (4 to 13), HR 1.11 (0.90 to 1.37) • 5-day R: 6 (5 to 10); HR 1.18 (0.96 to 1.45) • C: 7 (4 to 15) 8. **Time to modified recovery; median (25% to 75%), HR (95% CI)** • 10-day R: 7 (4 to 17), HR 1.10 (0.90 to 1.36) • 5-day R: 6 (4 to 9), HR 1.19 (0.96 to 1.46) • C: 7 (4 to 14) 9. **Time to room air; median (25% to 75%), HR (95% CI)** • 10-day R: 4 (2 to 6), HR 1.93 (1.11 to 3.36) • 5-day R: 5 (3 to 7); HR 1.31 (0.79 to 2.18) • C: 6 (4 to 14)
Duration of hospitalisation	**Hospital discharges over time:** reported in figures.
Safety outcomes • Adverse events, any grade * Adverse events grade 3 to 4 • Serious adverse events	**Safety outcomes:** included in analysis (Analysis 1.9; Analysis 1.10; Analysis 1.11).
Wang 2020	

Table 5. Narrative summary of outcomes of included studies *(Continued)*

Study outcomes (time point, definition)	Reported outcome data
All-cause mortality 1. At up to day 28 2. Stratified by treatment duration: early treatment administration (≤ 10 days of symptom onset) versus late administration (> 10 days of symptom onset)	**All-cause mortality** 1. At up to day 28 included in analysis (Analysis 1.1). 2. All-cause mortality at up to day 28 by treatment duration included in analyses (Analysis 3.1).
Clinical status at day 7, 14, 28 with odds ratio (OR) 6-category scale: 1. Discharge (alive) 2. Hospital admission, not requiring supplemental oxygen 3. Hospital admission, requiring supplemental oxygen 4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation 5. Hospital admission, requiring ECMO or invasive mechanical ventilation 6. Death	**Clinical status at day 7, n/N (%)** 1. R: 4/154 (3) versus C: 2/77 (3) 2. R: 21/154 (14) versus C: 16/77 (21) 3. R: 87/154 (56) versus C: 43/77(56) 4. R: 26/154 (17) versus C: 8/77 (10) 5. R: 6/154 (4) versus C: 4/77 (5) 6. R: 10/154 (6) versus C: 4/77(5) • **OR (95% CI): 0.69 (0.41 to 1.17)** **Clinical status at day 14, n/N (%)** 1. R: 39/153 (25) versus C: 18/78 (23) 2. R: 21/153 (14) versus C: 10/78 (13) 3. R: 61/153 (40) versus C: 28/78 (36) 4. R: 13/153 (8) versus C: 8/78 (10) 5. R: 4/153 (3) versus C: 7/78 (9) 6. R: 15/153 (10) versus C: 7/78 (9) • **OR (95% CI): 1.25 (0.76 to 2.04)** **Clinical status at day 28, n/N (%)** 1. R: 92/150 (61) versus C: 45/77 (58) 2. R: 14/150 (9) versus C: 4/77 (5) 3. R: 18/150 (12) versus C: 13/77 (17) 4. R: 2/150 (1) versus C: 2/77 (3) 5. R: 2/150 (1) versus C: 3/77 (4) 6. R: 22/150 (15) versus C: 10/77 (13) • **OR (95% CI): 1.15 (0.67 to 1.96)**
Clinical improvement • 2-point reduction in patient's admission status on a 6-point ordinal scale, or live discharge from the hospital, whichever came first, at up to day 7, 14, 28 • Time to clinical improvement within 28 days after randomisation (2-point reduction in patient's admission status on a 6-point ordinal scale, or live discharge from the hospital, whichever came first)	**Clinical Improvement** 1. **Clinical improvement rates, n/N (%); rate difference (95% CI)** • Day 7: R: 4/158 (3) versus C: 2/78 (3); 0% (–4.3 to 4.2) • Day 14: R: 42/158 (27) versus C: 13/78 (23); 3.5% (–8.1 to 15.1) • Day 28: R: 103/158 (65) versus C: 45/78 (58); 7.5% (–5.7 to 20.7) 2. **Time to clinical improvement, median days (IQR); HR (95% CI)** • R: 21 (13 to 28) versus C: 23 (15 to 28); 1.23 (0.87 to 1.75)
Clinical worsening • Time to clinical deterioration, defined as a 1-category increase or death.	• **Time to clinical deterioration, HR (95% CI):** 0.95 (0.55 to 1.64)

Table 5. Narrative summary of outcomes of included studies *(Continued)*

Duration of respiratory support 1. Duration of invasive mechanical ventilation 2. Duration of oxygen therapy	1. **Duration of invasive mechanical ventilation, days (IQR); difference (95% CI)** • R: 7 (4 to 16) versus C: 15.5 (6 to 21); −4 (−14 to 2) * In survivors: R: 19 (5 to 42) versus C: 42 (17 to 46); 12 (−41 to 25) * In non-survivors: R: 7 (2 to 11) versus C: 8(5 to 16); −2.5 (−11 to 3) 2. **Duration of oxygen support, days (IQR); difference (95% CI)** • R: 19 (11 to 30) versus C: 21 (14 to 30); −2 (−6 to 1)
Duration of hospitalisation • Duration of hospital stay • Time from random group assignment to discharge	• **Median duration of hospitalisation, days (IQR); difference (95% CI)** * R: 25 (16 to 38) versus C: 24 (18 to 36); 0 (−4 to 4) • **Median time to discharge, days (IQR); difference (95% CI)** * R: 21 (12 to 31) versus C: 21 (13.5 to 28.5); 0 (−3 to 3)
Viral clearance • Undetectable viral RNA on the nasopharyngeal and oropharyngeal swab taken at baseline and day 3, 5, 7, 10, 14, 21, 28 • Viral RNA load over time from baseline by quantitative PCR on the upper respiratory tract and lower respiratory tract and by duration of illness (≤ 10 days versus > 10 days) in the viral-positive population	• **Viral clearance** at baseline and day 3, 7, 14 included in analysis (Analysis 1.8). • **Viral load** over time reported in figures.
Safety outcomes • Adverse events, any grade * Adverse events grade 3 to 4 • Serious adverse events	• **Safety outcomes:** included in analysis (Analysis 1.9; Analysis 1.10; Analysis 1.11).
WHO Solidarity Trial Consortium 2021	
Study outcomes (time point, definition)	**Reported outcome data**
All-cause mortality 1. At up to day 28 2. In-hospital mortality (i.e. death during the original hospitalisation; follow-up ceased at discharge), regardless of whether death occurred before or after day 28 3. Time-to-event 4. Cardiac death in hospital	1. **All-cause mortality** at up to day 28 included in analysis (Analysis 1.1). 2. **In-hospital mortality:** included in analysis (Analysis 1.2); stratification by: a. gender; b. age: included (Analysis 2.1); c. prior days of hospitalisation; d. respiratory support at entry: included (Analysis 4.1); e. radiological record; f. pre-existing**conditions, n/N; rate ratio (99% CI):** • diabetes: R: 98/707 versus C: 86/666; 0.99 (0.67 to 1.45); • heart disease: R: 77/571 versus C: 75/567; 1.04 (0.68 to 1.58); • chronic liver disease: R: 7/36 versus C: 6/41; 1.82 (0.35 to 9.45); • chronic lung disease: 25/151 versus C: 19/145; 1.15 (0.52 to 2.54); • asthma: R: 20/139 versus C: 15/139; 1.27 (0.52 to 3.10). g. steroid use; h. geographic location. 3. **Time-to-event mortality** included in analyses (Analysis 1.3). 4. **Cardiac death** reported in figures.
Clinical worsening	**Initiation of mechanical ventilation:** included in analysis (Analysis 1.4).

Table 5. Narrative summary of outcomes of included studies *(Continued)*

• Initiation of mechanical ventilation (non-invasive and invasive ventilation) in participants not ventilated at entry	
Duration of hospitalisation	**Time to discharge** reported in figures**.**
• Time to discharge alive and stratified by respiratory support at entry	

Abbreviations
ALT = alanine transaminase
AST = aspartate transaminase
C = control
CI = confidence interval
ECMO = extracorporeal membrane oxygenation
HR = hazard ratio
IMV = invasive mechanical ventilation
IQR = interquartile range
NIV = non-invasive mechanical ventilation
OR = odds ratio
PCR = polymerase chain reaction
R = remdesivir
RNA = ribonucleic acid
SD = standard deviation

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register

Search string: remdesivir* OR GS5734 OR "GS 5734"

Study characteristics:
1) "Intervention assignment": "Randomised" OR "Unclear"
2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover" OR "Unclear" OR "Other"

= 193 references

Web of Science Core Collection (Advanced search)

#1 TI=(remdesivir* OR GS5734 OR "GS 5734") OR AB=(remdesivir* OR GS5734 OR "GS 5734")

#2 TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3 #1 AND #2

#4 TI=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

#5 #3 AND #4

Indexes=SCI-EXPANDED, ESCI Timespan=1945-2021

= 377 references

WHO COVID-19 Global literature on coronavirus disease

(remdesivir* OR GS5734 OR "GS 5734") AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

without MEDLINE and PubMed = 352 references

HISTORY

Review first published: Issue 8, 2021

CONTRIBUTIONS OF AUTHORS

KA: methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript.

FG: clinical expertise, study selection, data extraction and assessment, conception and writing of the manuscript.

KD: methodological expertise, study selection, data extraction and assessment.

AM: clinical expertise, data extraction and assessment, writing of the manuscript.

VT: clinical expertise, study selection, data extraction and assessment, writing of the manuscript.

VP: methodological expertise and advice, data extraction and assessment, conception and writing of the manuscript.

MIM: Information Specialist, development of the search strategy, writing of the manuscript.

MS: clinical expertise and advice, writing and proofreading of the manuscript.

CB: methodological expertise and advice, data extraction and assessment, conception, writing and proofreading of the manuscript.

FF: clinical expertise and advice, data extraction and assessment, conception, writing and proofreading of the manuscript.

DECLARATIONS OF INTEREST

KA: is member of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

FG: works as an Intensive Care Medicine Consultant and is member of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

KD: is member of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

AM: none known.

VT: works as an Intensive Care Medicine Consultant and is member of the CEOsys project (no direct funding).

VP: is member of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

MIM: is member of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

MS: has no known conflicts of interest to declare.

CB: none known.

FF: works as an Intensive Care Medicine Consultant and is member of the CEOsys project (no direct funding).

SOURCES OF SUPPORT

Internal sources

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  Department of Infectious Diseases and Respiratory Medicine
- University Hospital Leipzig, Germany

  Department of Anesthesiology and Intensive Care Medicine

External sources

- Federal Ministry of Education and Research, Germany

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of outcome measures

We specified outcomes regarding effectiveness and safety of remdesivir for individuals with COVID-19 and either moderate to severe or mild to asymptomatic disease after a guideline consortium (CEOsys) that took place after protocol registration. This approach was implemented in all reviews of CEOsys. We created outcome categories and added/specified the following outcomes for hospitalised participants with moderate or severe COVID-19, as follows.

- **All-cause mortality** at day 28, day 60, time-to-event, and at hospital discharge.
- **Clinical status**, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at day 28, day 60, and up to longest follow-up, including:
  - improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving participants;
    - ☐ ventilator-free days;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving participants;
    - ☐ duration to liberation from supplemental oxygen.
  - worsening of clinical status:
    - ☐ new need for mechanical ventilation;
    - ☐ new need for invasive mechanical ventilation;
    - ☐ new need for non-invasive mechanical ventilation or high-flow oxygen;
    - ☐ new need for oxygen by mask or nasal prongs.
- Need for dialysis at up to 28 days.
- **Quality of life**, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and the longest follow-up available.
- Need for admission to intensive care unit (ICU).
- Duration of ICU length of stay, or time to discharge from ICU.
- Duration of hospitalisation, or time to discharge from hospital.
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days.
- **Serious adverse events**, defined as number of participants with event.

- **Adverse events** (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event.

We combined three different types of advanced respiratory support (high-flow oxygen, non-invasive mechanical ventilation, and invasive mechanical ventilation) as one outcome measure with the term 'mechanical ventilation' for the following reasons.

- Their application in clinical routine usually gives indirect evidence about a clinically relevant worsening of organ functions in an individual patient.
- Their application is accompanied by a need for higher level of monitoring and care (e.g. admission to ICU).
- For the individual patient, the application of each of these advanced respiratory support devices means a relevant loss of independence and quality of life, compared to application of low-flow oxygen therapy or hospitalisation without any respiratory support.

Assessment of heterogeneity

We clarified our approach to exploring heterogeneity. We intended to conduct subgroups by type of respiratory support at baseline irrespective of the amount of statistical varaiation observed between the studies. We used sensitivity analysis rather than subgroup analysis to explore heterogeneity if the I square was over 80%.

Types of subgroup analyses

We expanded subgroup analysis, and additionally plan to conduct separate analysis if more data become available in the next updates of this review, for the following.

- Age of participants (divided into applicable age groups, e.g. 18 to 65 years, 65 to 79 years, 80 years and older).
- Pre-existing conditions (e.g. diabetes, respiratory disease, hypertension, immunosuppression, obesity, cardiac injury).
- Timing of first dose administration with illness onset.
- Severity of condition:
  * no oxygen versus low-flow oxygen versus mechanical ventilation (including high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation).
- Duration of remdesivir application:
  * 5-day course of remdesivir versus 10-day course of remdesivir.

Although we contacted all study authors, especially in terms of detailed description of the extent of respiratory support (e.g. low- versus high-flow oxygen, non-invasive versus invasive mechanical ventilation), there remained differences in the reporting of severity of illness and incomplete data sets, which resulted in a relevant obstacle to the planned subgroup analysis.

Living systematic review considerations

Our Information Specialist (MIM) will provide us with new search records weekly, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Cochrane LSR). We will manually check platform trials that were previously identified and listed as 'studies awaiting classification' for additional treatment arms. We will wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We will consider one or more of the following components to inform this decision.

- Findings that change the estimated effect of one or more prioritised outcomes.
- Findings that change the credibility (e.g. GRADE rating) of the estimated effect of one or more prioritised outcomes.
- New settings, populations, interventions, comparisons, or outcomes studied.

In case of emerging policy relevance because of global controversies around the intervention, we will consider republishing an updated review even though our conclusions remain unchanged. We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (e.g. when additional comparisons, interventions, subgroups or outcomes, or new review methods become available).

NOTES

Parts of the review's Methods section are adopted from templates of Cochrane Haematology and a similar protocol published by Piechotta 2020, and the corresponding review (Chai 2020).