Use of remdesivir in patients with COVID-19: a systematic review and meta-analysis

Suzana E Tanni[1], Antonio Silvinato[2], Idevaldo Floriano[3], Hélio A Bacha[4], Alexandre Naime Barbosa[5], Wanderley M Bernardo[6]

1. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.
2. Medicina Baseada em Evidências, Associação Médica Brasileira, São Paulo (SP) Brasil.
3. Medicina Baseada em Evidências, Cooperativa Baixa Mogiana, Mogi-Guaçu (SP) Brasil.
4. Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.
5. Departamento de Infectologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.
6. Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

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ABSTRACT

Objective: Studies in the literature regarding the use of remdesivir to treat COVID-19 patients have shown conflicting results. This study sought to answer questions related to the use of remdesivir for the treatment of patients hospitalized with moderate to severe COVID-19. **Methods:** This was a systematic review and meta-analysis including phase 3 randomized clinical trials (RCTs) and observational cohort studies selected from various databases, comparing patients hospitalized with moderate to severe COVID-19 receiving remdesivir and controls. **Results:** A total of 207 studies were retrieved, 9 of which met the eligibility criteria and were included in the study. The meta-analysis using RCTs alone showed no statistically significant differences regarding mortality or use of mechanical ventilation/extracorporeal membrane oxygenation between remdesivir and control groups, and the quality of evidence was moderate and low, respectively. The use of remdesivir increased the recovery rate by 6% (95% CI, 3-9); p = 0.004) and the clinical improvement rate by 7% (95% CI, 1-14); p = 0.02). Additionally, no significant differences in mortality were found between remdesivir and control groups when the meta-analysis used observational cohort studies alone (risk difference = −0.01 (95% CI, −0.02 to 0.01; p = 0.32), the quality of evidence being moderate, and the risk of adverse events was 4% ([95% CI, −0.08 to 0.01]; p = 0.09). **Conclusions:** The use of remdesivir for the treatment of patients with moderate to severe COVID-19 had no significant impact on clinically important outcomes.

Keywords: Antiviral agents; COVID-19; SARS-CoV-2.

INTRODUCTION

In March of 2020, the WHO declared that the current COVID-19 pandemic had spread worldwide, with 200,840,000 people being infected by the new SARS-CoV-2 and resulting in 4,265,000 deaths.[1] In Brazil, until August of 2021, there were 20,026,000 diagnosed cases and 559,607 deaths,[2] with a mortality rate of 3.81%. An increased risk of mortality is associated with the presence of comorbidities and the need for mechanical ventilation.[3]

The main mechanism underlying the development of ARDS is related to the binding of the viral surface glycoprotein, called a spike glycoprotein, to angiotensin-converting enzyme 2, the most abundant receptor in alveolar type II epithelial cells in the lungs, allowing viral entry.[4]

Remdesivir is an intravenous broad-spectrum antiviral drug developed in 2017 as a compassionate treatment option for the Ebola virus infection and was later tested for Middle East respiratory syndrome and SARS coronavirus.[5] Remdesivir is a direct-acting nucleotide-analog prodrug that inhibits RNA by incorporating triphosphates and interfering with viral RNA polymerase activity.[6] The in vitro efficacy of remdesivir against SARS-CoV-2 has previously been demonstrated.[7] In a rhesus monkey model of SARS-CoV-2 infection, treatment with remdesivir, which was started shortly after inoculation, resulted in lower viral load in the lungs and reduced lung damage in comparison with control animals.[8]

Remdesivir has been approved by the U.S. Food and Drug Administration for use in hospitalized adult and pediatric patients (≥ 12 years and weighing ≥ 40 kg) infected with SARS-CoV-2 and has further received conditional marketing authorization from the European Medicines Agency for use in patients with SARS-CoV-2-related pneumonia receiving supplemental oxygen. In Brazil, remdesivir was approved by the Brazilian National Health Surveillance Agency for use in hospitalized COVID-19 patients not on mechanical ventilation. However, the existing evidence from systematic reviews and meta-analyses are conflicting[9-11] and justify a living systematic review approach. Therefore, this systematic review sought to identify, describe, evaluate, and synthesize evidence regarding clinical outcomes of the use of remdesivir in hospitalized COVID-19 patients.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[12]

Correspondence to:
Suzana E Tanni. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Distrito de Rubião Junior, s/n, CEP 18618-970, Botucatu, SP, Brasil.
Tel.: 55 14 3811-1171. Email: suzanapneumo@gmail.com
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Eligibility criteria

The protocol of this study was based on the PICO methodology (Patients of interest, Intervention to be studied, Comparison of intervention, and Outcome of interest). Therefore, the PICO framework in the present study was Patients: adult patients with COVID-19; Intervention: use of remdesivir; Comparison: comparison between standard of care (SOC) and placebo; and Outcomes: all-cause mortality rate in 29 days, recovery rate in 29 days, patient clinical improvement rate in 29 days, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO), and adverse events. Intermediate outcomes, such as length of hospital stay (in days), were excluded.

Phase 3 randomized controlled trials (RCTs) and observational cohort studies with at least 24 days of follow-up were considered eligible for the study. We imposed no restrictions on the date of publication, language, or full-text availability.

Information sources and search strategy

Two of the authors developed a search strategy that was revised and approved by the team, selected information sources, and systematically searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Specific search strategies were used for each database: ("COVID-19" OR "COVID" OR "coronavirus" OR "SARS-CoV-2") AND ("remdesivir" OR "Adenosine nucleoside triphosphate analog" OR "Adenosine Monophosphate") AND (Therapy/narrow[filter] OR Prognosis/narrow [filter] OR "Comparative study" OR "Comparative studies"). Cochrane Central Register of Controlled Trials: (COVID-19 OR COVID OR CORONAVIRUS OR SARS-CoV-2) AND (remdesivir). The search strategy included studies published until October 18, 2021.

Study selection

Two independent researchers selected and extracted the data from the studies included. First, the articles were selected on the basis of their titles and abstracts. Second, full texts were evaluated to be included or excluded, and disagreements were resolved by consensus.

Data collection and investigated outcomes

Data regarding authorship, year of publication, patient description, interventions (remdesivir or control), absolute numbers of each outcome, and follow-up period were extracted from the studies.

Risk of bias and quality of evidence

The risk of bias for RCTs was assessed using the Cochrane risk-of-bias (RoB 2)[13,14] tool, as were other fundamental elements, which were expressed as very serious, serious, or not serious. For cohort studies, the risk of bias was assessed using the current tool recommended by the Cochrane Collaboration to estimate the effectiveness and safety of nonrandomized interventional studies—Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I).[15] ROBINS-I assesses seven domains of bias, classified by the time of occurrence. The assessment of risk of bias was conducted by two independent reviewers, and, in case of disagreement, a third reviewer deliberated on the assessment. The quality of evidence was extrapolated from the risk of bias and was described by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) terminology as very low, low, or high; for meta-analyses, the quality of evidence was described by the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada) as very low, low, moderate, or high.

Synthesis of results and analysis

Categorical outcomes were expressed by group (remdesivir or control), number of events, and calculated risk (in %) for each group (by dividing the number of events by the total number of patients in each group). If the risk difference between the groups was significant, a 95% CI was expressed on the basis of the number needed to treat (NNT) or the number needed to harm. We used the fixed-effect or random-effect model in the meta-analysis to evaluate the effect of remdesivir vs. control on the outcomes when these data were available in at least two RCTs or observational cohort studies. The effects of meta-analyses were reported as risk differences (RDs) and corresponding 95% CIs; a 95% CI including the number 0 in its range meant that there was no difference in the outcome effect between the remdesivir and control arms. The use of RD shows the absolute effect size in the meta-analysis when compared with the relative risk or odds ratio, and this technique can be used when the binary outcome is zero in both study arms. The heterogeneity of effects among studies was quantified using the I^2 statistic ($I^2 > 50\%$ indicates high heterogeneity). For the meta-analysis, we used the Review Manager software, version 5.4 (Cochrane, Oxford, United Kingdom). The results were presented using a methodological design (RCT or observational cohort study).

RESULTS

A total of 207 studies were retrieved from the selected databases (Figure 1). After eliminating duplicates and including studies that met the eligibility criteria, 14 studies were selected for full-text assessment. Of these, 5 were excluded (Figure 1); therefore, six RCTs[16-21] and three observational cohort studies were selected.[22-24] The characteristics (Table 1), results, risk of bias, quality of evidence, and synthesis of evidence of these studies are described below (Tables 2-4). No publication bias was identified.

The total population comprised 12,379 hospitalized moderate-to-severe COVID-19 patients (8,044 from the six RCTs and 4,335 from the three observational cohort studies); 5,722 patients received remdesivir,

and 6.657 received SOC or placebo. In regards to the risk of bias in the RCTs,[16-21] two had randomization and blinded allocation, showing a risk of bias,[17,20] four were single-blinded, with no blinding of the observer,[16-19] and one RCT did not use intention-to-treat analysis,[17] which was considered a risk of bias (Table 3).

Regarding the risk of bias in the three nonrandomized studies, only one had a moderate bias due to missing data. Overall, the studies were considered to have a low risk of bias (Figure 2 and Table 4).[22-24]

Qualitative description of included results

Beigel et al.[16] conducted a placebo-controlled RCT including adult patients hospitalized with COVID-19 and pulmonary impairment in the USA, Denmark, United Kingdom, Greece, Korea, Mexico, Spain, Japan, and Singapore. The patients were stratified according to the severity of pulmonary impairment (use of mechanical ventilation or supplemental oxygen). Intervention was treatment with remdesivir 200 mg i.v. on day 1, followed by remdesivir 100 mg i.v. from days 2 to 10 or until discharge/death. The primary outcome was time to recovery, defined on the basis of an 8-point ordinal scale (1: not hospitalized and no limitations of activities; 2: not hospitalized, with limitations of activities, home oxygen requirement, or both; 3. hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care—used if hospitalization was extended for infection control or other nonmedical reasons; 4. hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care—related to COVID-19 or other medical conditions; 5. hospitalized, requiring any type of supplemental oxygen; 6. hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7. hospitalized, receiving invasive mechanical ventilation or ECMO; and 8. death). Time to recovery was defined as the first day, during the 28-day follow-up period after enrollment, on which a patient met the criteria for category 1, 2, or 3. Secondary outcomes were time to improvement of one category and of two categories from the baseline ordinal score; the incidence and duration of new oxygen use, of noninvasive ventilation or high-flow oxygen, and of invasive ventilation or ECMO; number of days of hospitalization up to day 29; and mortality at 14 and 28 days after enrollment. Safety outcome

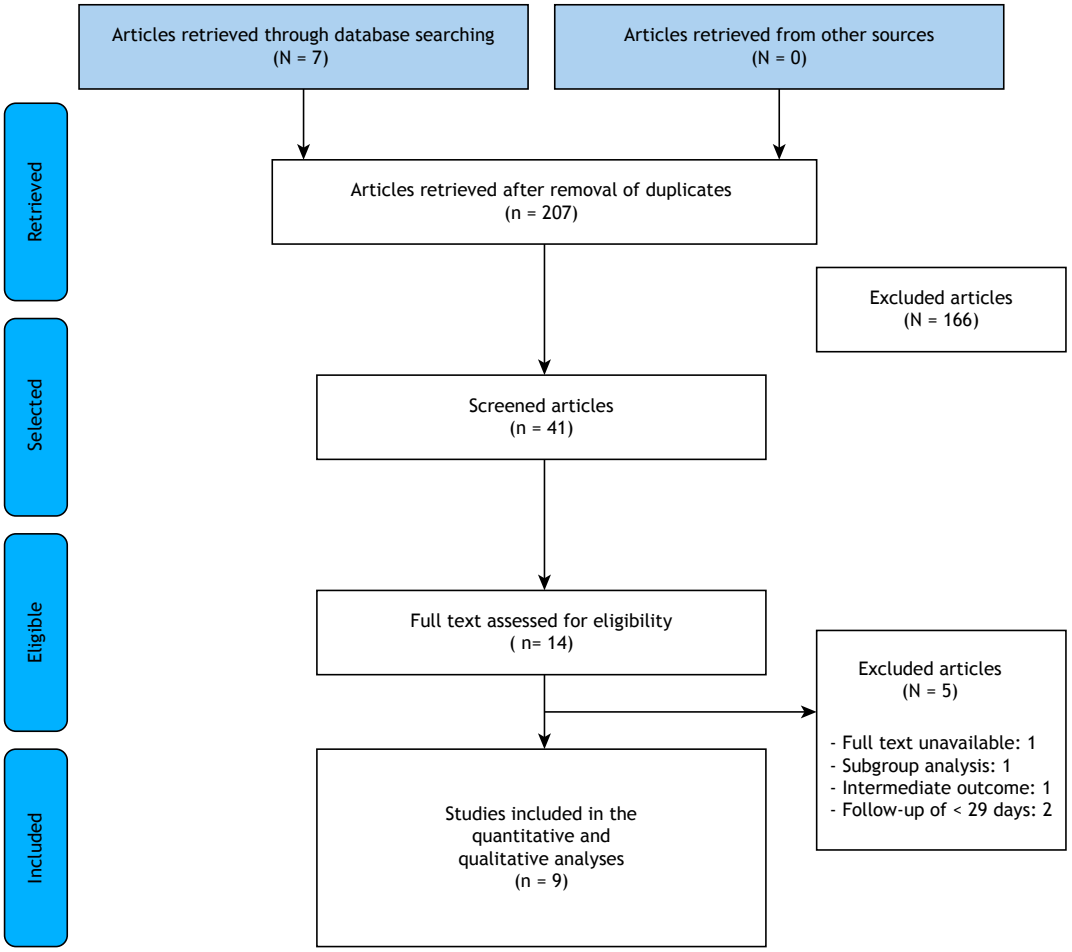


Figure 1. Flow chart of study selection based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12]

Table 1. Description of the studies included in the meta-analysis.

Study	Design	Population	Intervention	Comparator	Outcome	Follow-up
Beigel et al.[16]	RCT	Adults hospitalized with COVID-19 with pulmonary impairment Different severity levels of COVID-19	(N = 541) Remdesivir: 200 mg i.v. on day 1, followed by 100 mg on days 2-10 or until discharge or death	(N = 521) Placebo	Mortality in 15 and 29 days Mechanical ventilation or ECMO Time to recovery (discharge or hospitalization for infection control) Clinical improvement (recovery scale) Severe adverse events	29 days
Spinner et al.[19]	RCT	Patients hospitalized with SARS due to COVID-19 (pulmonary abnormalities and SpO_2 < 94% on room air = moderate to severe disease)	(N = 197) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-10 (N = 199) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-5	(N = 200) Standard of care corticosteroid, hydroxychloroquine, azithromycin, lopinavir-ritonavir	Mortality Mechanical ventilation or ECMO Recovery rate (recovery scale) Clinical improvement (recovery scale) Severe adverse events	28 days
Wang et al.[20]	RCT	Adult patients hospitalized with COVID-19 and onset of symptoms by 12 days SpO_2 < 94% on room air, PaO_2/FIO_2 ratio < 300, or radiological viral pneumonia Severe COVID-19	(N = 158) Remdesivir: 200 mg i.v. on ICU day 1, followed by 100 mg i.v. on days 2-10 Concomitant use of lopinavir-ritonavir, interferon, and corticosteroids	(N = 79) Placebo	Mortality Clinical improvement (recovery scale or discharge) Severe adverse events	28 days
WHO Solidarity Trial Consortium et al.[18]	RCT	Adult (≥ 18 years) patients hospitalized with COVID-19 Different severity levels of COVID-19	(N = 2,750) Remdesivir: 200 mg on day 0, followed by 100 mg on days 1-9	(N = 4,088) Standard of care, corticosteroids, convalescent plasma, anti-IL-6 drug	Mortality Mechanical ventilation or ECMO	28 days

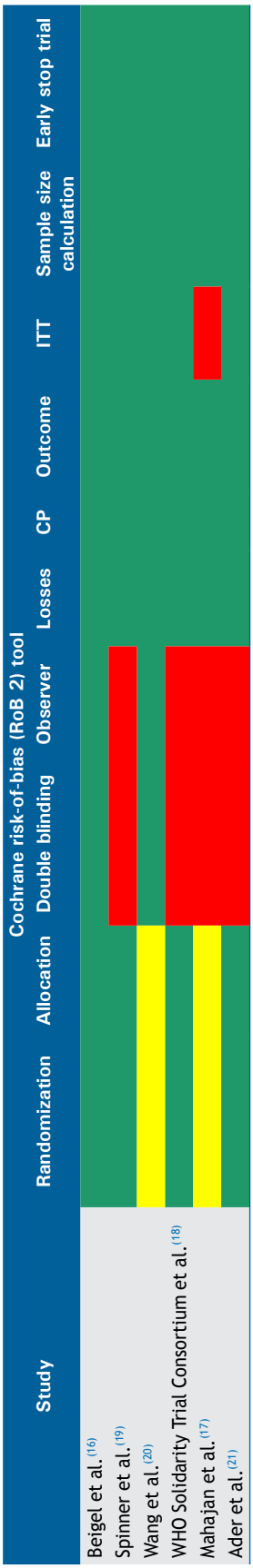
Continue...▶

Table 1. Description of the studies included in the meta-analysis. (Continued...)

Study	Design	Population	Intervention	Comparator	Outcome	Follow-up
Mahajan et al.[17]	RCT	Adult (18-60 years) patients hospitalized with moderate to severe COVID-19 within the last 4 days with viral pneumonia, RR > 24 breaths/min, and SpO_2 < 94%, not on mechanical ventilation or presenting with multiple organ failure	(N = 34) Remdesivir: 200 mg i.v. on day 1, followed by 100 mg on days 2-5 Concomitant use of heparin and corticosteroids	(N = 36) Standard of care, corticosteroids, heparin	Mortality Mechanical ventilation Recovery rate (recovery scale) Adverse events	24 days
Ader et al.[21]	RCT	Adult (≥ 18 years) patients hospitalized with moderate to severe COVID-19, based on clinical assessment and SpO_2 < 94% or requiring supplemental oxygen, noninvasive ventilation, or mechanical ventilation	(N = 414) Remdesivir: 200 mg i.v. on day 1, followed by 100 mg i.v. on days 2-10	(N = 418) Standard of care, corticosteroids, heparin	Clinical status at days 15 and 29 Time to improvement Time to hospital discharge Mortality	29 days
Kalligeros et al.[22]	OCS	Adult patients hospitalized with COVID-19 and SpO_2 < 94% or requiring supplemental oxygen Pulmonary abnormalities, creatinine clearance > 50 mL/min, AST and ALT < 5 upper limit unit of normal	(N = 99) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-10	(N = 125) Standard of care, corticosteroids, convalescent plasma, hydroxychloroquine	Mortality Clinical improvement Length of hospital stay	28 days
Ohl et al.[23]	OCS	Positive test for SARS-CoV-2 within 14 days prior to or during hospitalization Creatinine clearance > 50 mL/min, AST e ALT < 5 upper limit unit of normal	(N = 1,172) Remdesivir	(N = 1,172) Standard of care, corticosteroid, hydroxychloroquine, azithromycin, heparin	Mortality Length of hospital stay	30 days
Olender et al.[24]	OCS	Adult (≥ 18 years) patients hospitalized with COVID-19, SpO_2 < 94% or requiring supplemental oxygen Pulmonary abnormalities, creatinine clearance > 50 mL/min, AST e ALT < 5 upper limit unit of normal	(N = 268) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-10	(N = 1,399) Standard of care, azithromycin, biologic agents, HIV protease inhibitors, hydroxychloroquine, ribavirin	Mortality	28 days

RCT: randomized clinical trial; and OCS: observational cohort study.

Table 2. Risk of bias of the randomized controlled trials included in the analysis.



CP: characteristic prognosis; and ITT: intention to treat.
Observation: red = risk of bias; yellow = not clear; green = no risk of bias.

measures included adverse events and serious adverse events.[16]

Mahajan et al.[17] conducted a single-center RCT including adult patients hospitalized with COVID-19 (confirmed RT-PCR within the last 4 days), RR > 24 breaths/min, SpO_2 < 94%, and no mechanical ventilation use or multiple organ failure. The intervention group received remdesivir 200 mg i.v. on day 1, followed by remdesivir 100 mg i.v. once a day from days 2 to 5. The outcomes were mortality, use of mechanical ventilation, and recovery rate.

The WHO Solidarity Trial Consortium et al.[18] conducted an RCT that included hospitalized COVID-19 patients ≥ 18 years of age who had neither been known to have received any trial drug nor were expected to be transferred elsewhere within the following 72 h. The trial drugs were remdesivir, hydroxychloroquine, lopinavir, and interferon. The controls for a drug were patients assigned to receive SOC at a time and place in which that drug was locally available. One of the intervention groups received remdesivir 200 mg i.v. on day 0 and remdesivir 100 mg from days 1 to 9. The primary objective was to assess the effects of the drug on in-hospital mortality, regardless of whether death occurred before or after day 28. Secondary outcomes were initiation of mechanical ventilation and length of hospital stay.[18]

Spinner et al.[19] conducted an RCT in the USA, Europe, and Asia using three different groups randomly assigned in a 1:1:1 ratio to receive up to a 5-day course of remdesivir, up to a 10-day course of remdesivir, or SOC. Randomization was not stratified. They included patients hospitalized with SARS due to COVID-19 infection (pulmonary abnormalities and SpO_2 < 94% on room air). All patients randomized to one of the remdesivir groups received 200 mg i.v. on day 1, followed by remdesivir 100 mg i.v., infused between 30 and 60 min, once a day on the subsequent days. Prespecified exploratory endpoints were time to recovery (improvement from a baseline score of 2-5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7); time to modified recovery (improvement from a baseline score of 2-4 to a score of 5-7, improvement from a baseline score of 5 to a score of 6-7, or improvement from a baseline score of 6 to a score of 7); time to clinical improvement (≥ 2-point improvement from baseline on the 7-point ordinal scale); time to improvement by 1 or more points; time to discontinuation of any oxygen support; and all-cause mortality.[19]

Wang et al.[20] conducted an RCT in ten hospitals in Wuhan, China, including adult patients hospitalized with COVID-19 and confirmed pneumonia by chest imaging, SpO_2 ≤ 94% on room air or PaO_2/FIO_2 ratio ≤ 300 mmHg, and symptom onset ≤ 12 days. The primary clinical endpoint was time to clinical improvement within 28 days after randomization. Clinical improvement was defined as hospital discharge or a 2-point reduction from baseline admission score on a 6-point ordinal scale (6: death; 5: hospital admission for ECMO or

Table 3. GRADE analysis of remdesivir compared with placebo/standard of care in patients hospitalized with moderate to severe COVID-19 in randomized clinical trials.

No. of studies	Study design	Certainty assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients: Remdesivir	Placebo/SOC	Effect: Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality in 29 days												
5	Randomized trials	very serious[a]	not serious	not serious	not serious	none	390/3669 (10.6%)	397/3543 (11.2%)	RR 0.94 (0.82 to 1.07)	7 fewer per 1,000 (from 20 fewer to 8 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Recovered patients in 29 days												
3	Randomized trials	very serious[b]	not serious	not serious	very serious[c]	none	579/768 (75.4%)	525/757 (69.4%)	RR 1.09 (1.03 to 1.15)	62 more per 1,000 (from 21 more to 104 more)	⊕⊕◯◯ LOW	IMPORTANT
Clinical improvement in 29 days												
2	Randomized trials	very serious[d]	not serious	not serious	very serious[c]	none	277/351 (78.9%)	211/278 (75.9%)	RR 1.10 (1.01 to 1.19)	76 more per 1,000 (from 8 more to 144 more)	⊕⊕◯◯ LOW	IMPORTANT
Mechanical ventilation or ECMO in 29 days												
5	Randomized trials	very serious[a]	very serious[e]	not serious	not serious	very serious[f]	354/3268 (10.8%)	375/3152 (11.9%)	RR 0.76 (0.46 to 1.26)	29 fewer per 1,000 (from 64 fewer to 31 more)	⊕◯◯◯ VERY LOW	IMPORTANT
very serious adverse events in 29 days												
3	Randomized trials	not serious	not serious	not serious	very serious[c]	None	169/880 (19.2%)	201/794 (25.3%)	RR 0.75 (0.63 to 0.90)	63 fewer per 1,000 (from 94 fewer to 25 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

GRADE: Grading of Recommendations Assessment, Development and Evaluation; SOC: standard of care; and RR: risk ratio.
Explanations
a. Three of the five studies were not blinded by the researcher. Two studies showed risk of bias related to randomization and allocation, with some concerns.
b. Two of the three studies were not investigator's blinded studies, and one study had a risk of bias for randomization and blind allocation, with some concerns.
c. Large confidence interval
d. One of the two included studies was not blinded by the researcher, and one had a risk of bias for randomization and blind allocation with some concerns.
e. High heterogeneity (I^2 = 71%).
f. Publication bias.

Table 4. GRADE analysis of remdesivir compared with placebo/standard of care in patients hospitalized with moderate to severe COVID-19 in observational cohort studies.

No. of studies	Study design	Risk of bias	Certainty assessment				No. of patients		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	SOC	Relative (95% CI)	Absolute (95% CI)		
Mortality in 28 days												
3	Observational study	not serious	Severe[a]	not serious	not serious	none	194/1639 (11.8%)	367/2696 (13.6%)	RR 0.85 (0.56 to 1.28)	20 fewer per 1,000 (from 60 fewer to 38 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

GRADE: Grading of Recommendations Assessment, Development and Evaluation; SOC: standard of care; and RR: risk ratio.
Explanations
a. High heterogeneity (I^2 = 76%).

mechanical ventilation; 4: hospital admission for noninvasive ventilation or high-flow oxygen therapy; 3: hospital admission for oxygen therapy; 2: hospital admission but not requiring oxygen therapy; and 1: discharged or having reached discharge criteria). Secondary outcomes were all-cause mortality at day 28 and frequency of invasive mechanical ventilation.[20]

Ader et al.[21] conducted an RCT in France, Belgium, Austria, Portugal, and Luxembourg. They included adult patients hospitalized with COVID-19 with evidence of rales or crackles on clinical examination and SpO_2 ≤ 94% on room air or requirement of supplemental oxygen, high-flow oxygen devices, noninvasive ventilation, or mechanical ventilation. Remdesivir was administered intravenously at a dose of 200 mg on day 1, followed by a dose of 100 mg (1-h infusion once daily for up to 10 days). The primary outcome measure was clinical status at day 15 as measured on the 7-point ordinal scale of the WHO Master Protocol (1: not hospitalized, no limitations on activities; 2: not hospitalized, limitations on activities; 3: hospitalized, not requiring supplemental oxygen; 4: hospitalized, requiring supplemental oxygen; 5: hospitalized, on noninvasive ventilation or high-flow oxygen devices; and 7. hospitalized, on invasive mechanical ventilation or ECMO). Secondary outcome measures were clinical status and change from baseline clinical status at day 29; time to improvement by 1-2 points as measured on the 7-point ordinal scale or hospital discharge by day 29; length of hospital stay; time to new mechanical ventilation; in-hospital mortality; and mortality at day 28.[21]

Kalligeros et al.[22] conducted an observational study in the USA including adult (≥ 18 years) patients hospitalized with COVID-19 ≤ 4 days prior and SpO_2 ≤ 94% or needing oxygen supplementation and presenting with pulmonary infiltrates. The patients received remdesivir 200 mg i.v. on day 1, followed by a daily maintenance dose of 100 mg from days 2 to 10 or until hospital discharge or death. The primary outcome was the impact of remdesivir on all-cause in-hospital mortality by day 28. Secondary outcomes were time to clinical recovery, time to clinical improvement, and time to discharge.

Ohl et al.[23] conducted a retrospective observational study including patients who tested positive for SARS-CoV-2 within 14 days prior to or during hospitalization at institutions pertaining to the U.S. Veterans Health Administration. The primary outcome was 30-day mortality from remdesivir treatment initiation.

Olender et al.,[24] based on an RCT and a longitudinal real-world study, conducted a prospective study including patients hospitalized with COVID-19 and SpO_2 ≤ 94% on room air or requiring supplemental oxygen and presenting with pulmonary infiltrates. The intervention group received remdesivir 200 mg on day 1, followed by remdesivir 100 mg/day either on days 2-5 or on days 2-10. The outcomes were clinical recovery after treatment initiation and 28-day all-cause mortality.

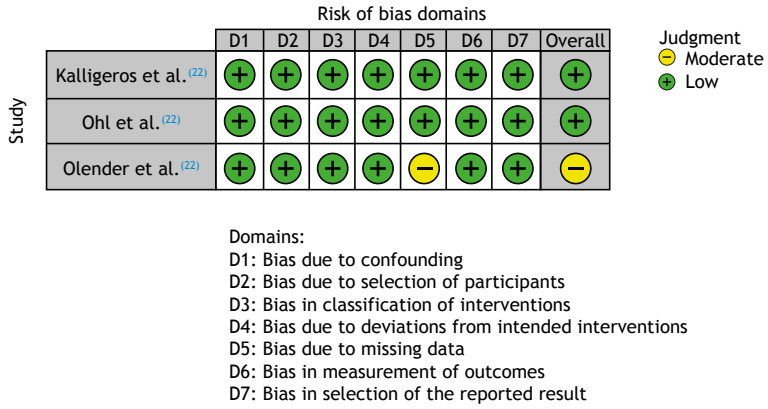


Figure 2. Risk of bias for nonrandomized studies.[a]
[a]In accordance with the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool.[15]

RCT results

Mortality

The analysis of 29-day mortality included six RCTs (8,044 patients).[16-21] No statistical difference was found between the remdesivir/SOC and SOC/placebo groups (RD = −0.01 [95% CI, −0.02 to 0.01]; p = 0.32; I^2 = 0%; Figure 3A). The quality of the evidence was moderate.

Recovery rate by day 29

The definitions of recovery differed among the studies. Beigel et al.[16] considered recovery when the patient had a score of 1-3 based on the criteria of an 8-point ordinal scale. Mahajan et al.[17] used a 6-point ordinal scale (1: does not require hospitalization; 2: hospitalized, not requiring supplemental oxygen; 3: hospitalized, requiring supplemental oxygen; 4: hospitalized, requiring high-flow oxygen or noninvasive ventilation; 5: hospitalized, requiring/receiving mechanical ventilation; and 6: death). Spinner et al.[19] used a 7-point ordinal scale whereby recovery was improvement from a baseline score of 2-5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7. Ader et al.[21] used the 7-point ordinal scale of the WHO Master Protocol.

Based on these four studies (N = 2,357),[16,17,19,21] the use of remdesivir/SOC, when compared with placebo/SOC, increased the recovery rate by 6% (RD = 0.06 [95% CI, 0.03-0.09]; p = 0.004; I^2 = 0%), and the NNT was 17 patients for 1 patient to show recovery (95% CI, 11-33; Figure 3B). However, the quality of evidence was low.

Clinical improvement rate in 29 days

Clinical improvement was defined according to the study protocol. Spinner et al.[19] considered an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death and 7 = hospital discharge). Wang et al.[20] used a variation of a 2-point reduction in the baseline 6-point ordinal scale score or hospital discharge, whichever came first.

Two studies evaluated the outcome of clinical improvement within 29 days (n = 629).[19,20] Comparing remdesivir/SOC and placebo/SOC groups, there was a 7% increase in the rate of patients with clinical improvement, favoring remdesivir (RD = 0.07 [95% CI, 0.01-0.14]; p = 0.02; I^2 = 0%; NNT = 14 [95% CI, 7-100]; Figure 3C). However, the quality of evidence was low.

Mechanical ventilation or ECMO in 29 days

Six studies were included to assess the combined outcome of mechanical ventilation or ECMO use within 29 days (n = 7,252). No statistically significant difference was found between remdesivir/SOC and placebo/SOC groups (RD = −0.02 [95% CI, −0.05 to 0.00]; p = 0.08; I^2 = 68%; Figure 3D). The quality of evidence was low.[16-21]

Severe adverse events in 29 days

Four studies, with a total of 2,498 participants, were used to assess severe adverse events.[1619-21] When comparing remdesivir/SOC and placebo/SOC groups, we found that remdesivir use had no influence on the risk of serious adverse events. The risk of adverse events was 4% (RD = −0.04 [95% CI, −0.08 to 0.01]; p = 0.09; I^2 = 41%; Figure 3E). The quality of evidence was moderate.

Observational cohort study results

Mortality

Three cohort studies evaluated mortality within 24-28 days, with a total of 4,335 participants.[22-24] No statistically significant difference was found between remdesivir/SOC and placebo/SOC groups (RD = −0.02 [95% CI, −0.07 to 0.03]; p = 0.37; I^2 = 76%; Figure 4). These studies had a moderate quality of evidence.

Quality of evidence of RCTs and observational cohort studies

The quality of evidence in the analysis of the remdesivir/SOC groups vs. control groups, including

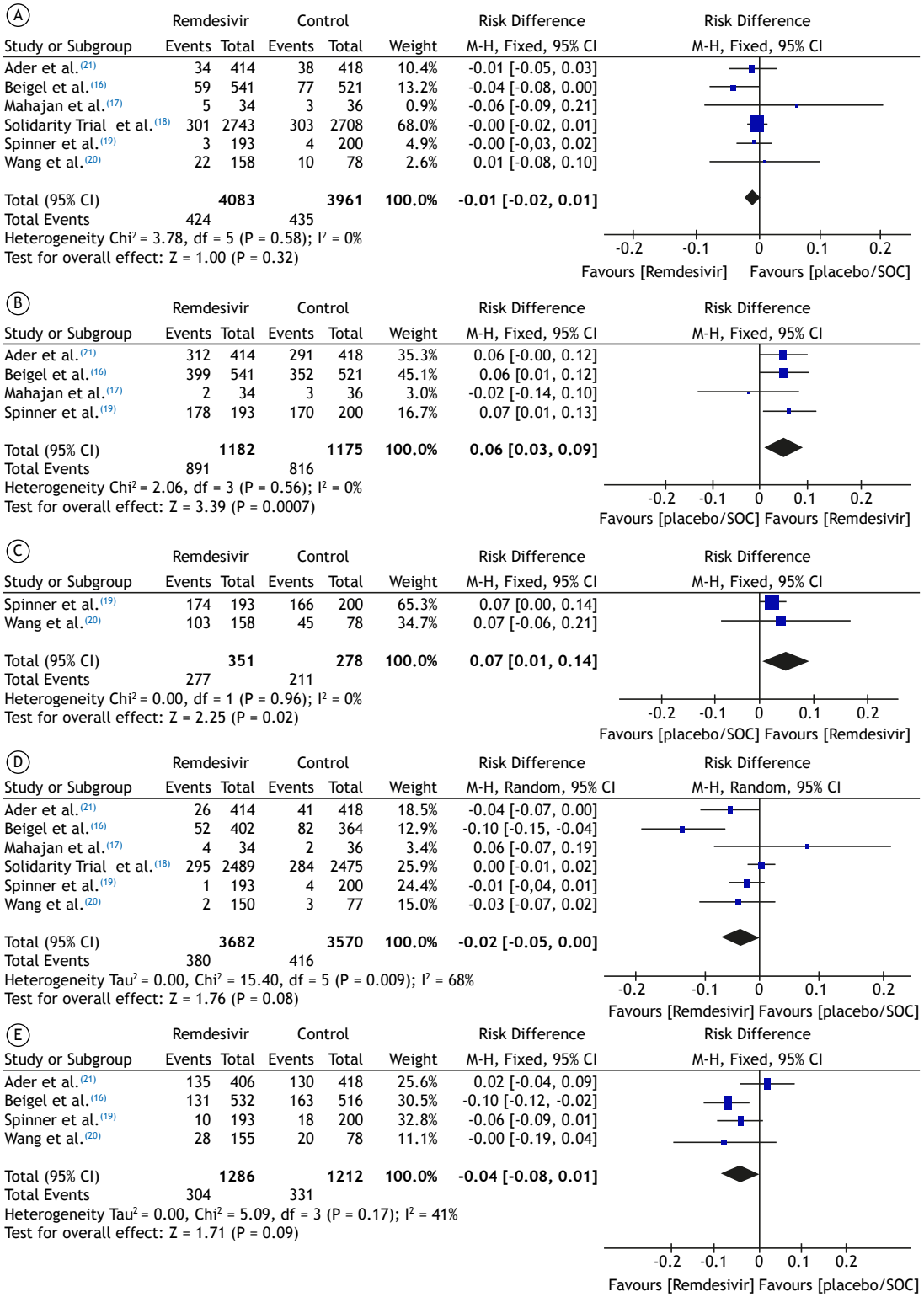


Figure 3. Meta-analyses and forest plots (based on randomized clinical trials) between intervention (remdesivir/standard of care [SOC]) and control (placebo/SOC) groups regarding mortality in 29 days (in A); patient recovery rate in 29 days (in B); clinical improvement rate in 29 days (in C); use of mechanical ventilation/extracorporeal membrane oxygenation in 29 days (in D); and severe adverse events in 29 days (in E). RDV: remdesivir; M-H: Mantel-Haenszel (method); and df: degrees of freedom.

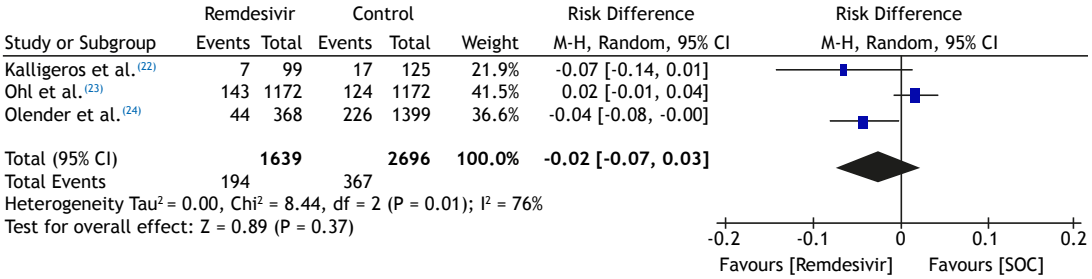


Figure 4. Meta-analysis and forest plot (based on observational cohort studies) between intervention (remdesivir/standard of care [SOC]) and SOC groups regarding mortality in 28 days. RDV: remdesivir; M-H: Mantel-Haenszel (method); and df: degrees of freedom.

only RCTs, varied according to the analyzed outcome during a follow-up period of up to 29 days, in accordance with the GRADE terminology: death (moderate), recovery rate (low), clinical improvement (low), and serious adverse events (moderate; Table 3).

The three cohort studies included only all-cause mortality as an outcome, allowing for the meta-analysis, and had a moderate quality of evidence within the 24-to 28-day follow-up period (Table 4).

DISCUSSION

The main results of this systematic review were that remdesivir had no effect on reducing mortality, the use of mechanical ventilation/ECMO, or severe adverse events in hospitalized patients with moderate to severe COVID-19. However, we identified increased rates of clinical improvement and recovery in those patients.

Regarding the mortality outcome, our results are similar to those of a previous systematic review published in the literature.[9,11,25,26] In studies that revealed a lower risk of mortality using remdesivir, we observed differences in methodological characteristics; those meta-analyses pooled observational studies together with RCTs or assessed the mortality rate on day 14.[10] These aspects can directly affect the results and influence treatment decisions. In the present systematic review, we used robust methods, such as RD, to consider the critical outcomes (mortality and use of mechanical ventilation) and demonstrated the direct effect of the intervention. Additionally, we divided the pooled results considering the design of the pooled studies.

With regard to clinical improvement and recovery rates, the use of remdesivir demonstrated a positive influence on hospitalized patients in the present meta-analysis. On the other hand, even with positive results, we need to consider the differences between studies that used different scales of disease severity that could directly affect the outcome response, leading to an uncertain benefit in clinical improvement. Different from our results, the literature consistently demonstrates a reduced rate of severe adverse events associated with the use of remdesivir,[9,25,26] which is a clinically important factor and should be considered when making treatment decisions. However, when we compare the importance of different outcomes, we must consider the patients' opinions. Even when the mortality rate is similar, knowledge of clinical improvement can influence treatment decisions.

The early use of remdesivir in patients hospitalized with moderate to severe COVID-19 can be relatively associated with clinical improvement and recovery rates. However, we need to evaluate this affirmation by considering the interactions of different treatments. A higher proportion of patients in the RCTs included in this systematic review received other COVID-19 treatment options, such as corticosteroids, convalescent plasma, and immunotherapy. The interaction of different pharmacological interventions and different respiratory support systems with comorbidities needs to be explored in the main results. However, this requires a greater number of patients because the subgroup analysis failed to demonstrate the efficacy of remdesivir in decreasing the mortality rate.[9] The transposition of this information to modify clinical practice needs to be balanced with the NNT, costs, and effects. In the case of low- and middle-income countries, the impact of high costs of COVID-19 treatment per patient needs to be considered using the best medical evidence.

The strength of this systematic review lies in the methodological characteristics adopted, with the separation of RCTs from observational cohort studies, revealing the influence of remdesivir use on the selected outcomes. The certainty of the present results is dependent on novel RCTs involving a larger population for analysis. Therefore, we cannot affirm whether the present results can be used as modifiers in the future. However, to reduce publication bias, we used a comprehensive search strategy. Nevertheless, this systematic review has limitations that need to be addressed.

In conclusion, the results of this systematic review demonstrated no benefit from the prophylactic use of remdesivir in the treatment of COVID-19.

FINAL CONSIDERATIONS

On the basis of the evaluation of the RCTs included in this systematic review, in patients hospitalized with moderate to severe COVID-19, the use of remdesivir/

SOC is equivalent to conventional treatment by day 29 and showed no differences regarding the risks of death or severe adverse events, the quality of evidence being moderate. However, an increase in the number of recovering patients by 6% (NNT = 17) was observed, but the quality of evidence was low. Furthermore, the number of patients showing clinical improvement increased by 7% (NNT = 14), but the quality of evidence was low. There was no difference in the risk of requiring mechanical ventilation/ECMO (low quality of evidence). On the basis of the evaluation of the observational cohort studies included in this systematic review, in patients hospitalized with moderate to severe COVID-19, treatment with remdesivir/SOC is equivalent to conventional treatment within 24-28 days and did not modify the risk of death, the quality of evidence being moderate.

AUTHOR CONTRIBUTIONS

SET, HAB, AN, and WMB: study concept and design. WMB, AS and IF: data collection, statistical analyses, and interpretation of data. WMB and SET: drafting of the manuscript. SET, HAB, AN, and WMB: critical review and approval of the final version.

CONFLICT OF INTEREST

None declared.

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