COVID-19

Evaluation of the Treatment Efficacy and Safety of Remdesivir for COVID-19: a Meta-analysis

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Abstract

Remdesivir is one of few FDA-approved treatments for severe cases of Coronavirus Disease 2019 (COVID-19). To better assess its efficacy and safety, we conducted a meta-analysis to systematically identify and synthesize existing findings. We conducted a comprehensive literature search among six electronic databases and unpublished studies. Random-effects meta-analyses were performed to summarize the risk ratio (RR) and rate estimates from eligible studies. Funnel plots, the Egger test, and the trim and fill analysis were used to detect publication bias. Thirteen eligible studies were included in this meta-analysis, giving a pooled sample size of 10,002 COVID-19 hospitalized patients (5068 administered remdesivir; 4934 control). Among patients on remdesivir, we synthesized mortality (15%, 95% confidence interval [CI]: 9%, 22%), clinical improvement (64%, 95% CI: 51%, 78%), recovery (70%, 95% CI: 57%, 83%), hospital discharge (74%, 95% CI: 60%, 87%), serious adverse effect (SAE) (21%, 95% CI:13%, 29%), and Grade 3 or 4 adverse effect (AE) (30%, 95% CI: 12%, 48%). Patients on remdesivir were 17% (RR: 0.83, 95% CI: 0.65, 1.06) less likely to die than those within the control group. Additionally, remdesivir had favorable outcomes in terms of clinical improvement, recovery, and hospital discharge. Lastly, non-mechanically ventilated patients had better overall clinical outcomes than mechanically ventilated patients. Remdesivir shows a moderate-favorable treatment efficacy among hospitalized COVID-19 patients with disproportionate impact among non-mechanically ventilated patients; however, a substantial proportion of COVID-19 patients may suffer from SAE or Grade 3 or 4 AE during the treatment course.

Keywords Remdesivir · COVID-19 · Treatment efficacy · Adverse effect

Background

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in December 2019 in China [1]. This outbreak rapidly developed into an international crisis that is now recognized as an ongoing, global pandemic with over a hundred million cases and millions of deaths [2]. The clinical presentation of COVID-19 varies from asymptomatic infection to critical illness with severe cases resulting in multi-organ failure that require intensive care unit (ICU) admission for mechanical ventilation, renal replacement therapy, and vasopressor support for refractory shock [1]. Further, studies on latent signs and symptoms of SARS-CoV-2 have found that 80–90% of patients present with ground-glass opacity (GGO) lesions regardless of disease severity [3, 4] and that infection induced immune inflammation could cause damage to the cardiovascular system [5, 6], heart [7], brain [8], liver [9, 10], and kidney [11]. Ultimately, these long-term effects present additional factors to consider when assessing the risk for permanent damage and reduced quality of life among COVID-19 patients.

Remdesivir (GS-5734), a viral RNA-dependent RNA polymerase (RdRp) inhibitor, can compete with native adenosine triphosphate (ATP) for incorporation into new RNA strands. This induces "chain termination" or inhibition of viral genome replication by means of premature termination of

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RNA synthesis, ultimately resulting in the suppression of virus replication [12]. Remdesivir has been demonstrated to suppress antiviral activity against a broad range of RNA viral infections, including coronavirus (SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) and filoviruses (Ebola) [13]. In a recent study, Wang and colleagues evaluated the *in vitro* activity of seven antiviral drugs against SARS-CoV2 and found that remdesivir was effective in controlling COVID-19 infection [14]. Given the promising results and rapidly worsening toll of the pandemic, remdesivir was approved for use on patients with severe COVID-19 under the Compassionate Use Act in January 2020.

The clinical condition of the first laboratory-confirmed COVID-19 patient significantly improved within 24 h of administration of remdesivir with no adverse side-effects observed [15]. Later, research confirming this initial observation was published — a study conducted by Grein *et al.* assessing clinical outcomes for COVID-19 patients in the USA, Europe, Canada, and Japan found that 36 of 53 (68%) hospitalized patients who received at least one dose of remdesivir experienced clinical improvement [16]. Further, a clinical trial conducted by the National Institutes of Health demonstrated that remdesivir could significantly reduce recovery time [17]. In response to these promising results, an emergency authorization for use of remdesivir on hospitalized patients with severe COVID-19 was approved on May 1, 2020. However, the clinical efficacy of remedisvir among COVID-19 hospitalized patients is unclear.

In June 2020, large-scale distribution made remdesivir available to hospitalized COVID-19 patients with severe disease status in the USA. Of the limited randomized controlled trials (RCTs) and single-arm studies (no control arm) evaluating the effect of remdesivir on COVID-19, very few report inconsistent results [[17–24]]. To better assess the overall effect of remdesivir on clinical outcomes for COVID-19, we conducted a meta-analysis to systematically identify trials and synthesize existing results.

Methods

Literature Search and Study Selection

In this study, we conducted a systematic literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. We identified studies that assessed the treatment effect of remdesivir on COVID-19 patients, published from June 18th, 2020 to March 8th, 2021. Six electronic databases were searched: Pubmed (National Center for Biotechnology Information, Bethesda MD), Web of Science (Thomson Scientific Technical Support, New York), Proquest (Cambridge Information Group), Embase (Elsevier), Google Scholar, and ScienceDirect (Elsevier). We extended our search to preprint

materials using medRxiv and to RCTs using remdesivir to treat COVID-19 patients at ClinicalTrials.org. Databases were searched beginning on June 18, 2020, and literature was extracted on March 8th, 2021 by JT and RA.

The search strategy was adjusted for each database using the following combination of MeSH terms and/or keywords, "Remdesivir OR GS-5734" AND "COVID-19 OR SARS-CoV-2". The full PubMed search strategy is described in the appendix.

Study Criteria and Selection

We determined study eligibility using the following inclusion criteria: (1) was an RCT, cohort study, chart review, or single arm prospective study; (2) assessed the treatment effect of remdesivir; (3) used COVID-19 patients as the study population; (4) measured clinical improvement, hospital discharge, recovery, mortality, or adverse events; and (5) provided sufficient information to calculate effect size (ES) estimates.

Studies identified in the literature search were imported into EndNote 8.0 (Thomson Reuters Corporation, New York). After removing duplicates, we conducted title screening and excluded irrelevant articles. We reviewed the abstracts of the remaining articles, and only studies that mentioned the use of remdesivir on COVID-19 patients were chosen for full-text screening. JT and RA conducted the screening and selection process independently.

Data Extraction

For eligible studies, we used a standardized approach to extract the following information: first author's name, year of publication, study period, study country, study design, sample size, study population/eligibility criteria, remdesivir dose duration, method of drug delivery, control group duration, and outcomes of interests. Outcomes of interest included clinical improvement (2 points increase on 6-point scale), recovery, all-cause mortality, serious adverse events (SAE), and grade 3 or 4 adverse events (AE). Recovery was defined as an improvement to one of two outcomes: hospital discharge or removal from supplementary oxygen [18, 19, 23]. Adverse events were defined as grade 3 and 4 adverse events and serious adverse events. We extracted the total number of patients and number of patients with outcomes of interest in each group. JT and RA extracted information indecently and reached agreement after the data extraction.

Assessment of Risk of Bias

We used the Cochrane Collaboration's tool to assess risk of bias in the meta-analysis (http://handbook-5-1.cochrane.org/). We assessed risk of bias in different domains, including selection bias (i.e., random sequence generation and allocation

concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). JT and RA performed the risk of bias assessment and achieved agreement.

Statistical Methods

To account for variation in studies' reported effect sizes, we calculated and synthesized crude risk ratios (RRs) in our meta-analysis. We used random-effects meta-analyses using inverse variance weights to pool RRs among eligible studies. The natural logarithm of RRs and 95% confidence intervals (CIs) were used for synthesis and then transformed back for ease of interpretation. For the percentage of clinical improvement, recovery, hospital discharge, death, SAE, and grade 3 or 4 AE, percentages and standard error were used for synthesis. Forest plots were used to display the synthesized results.

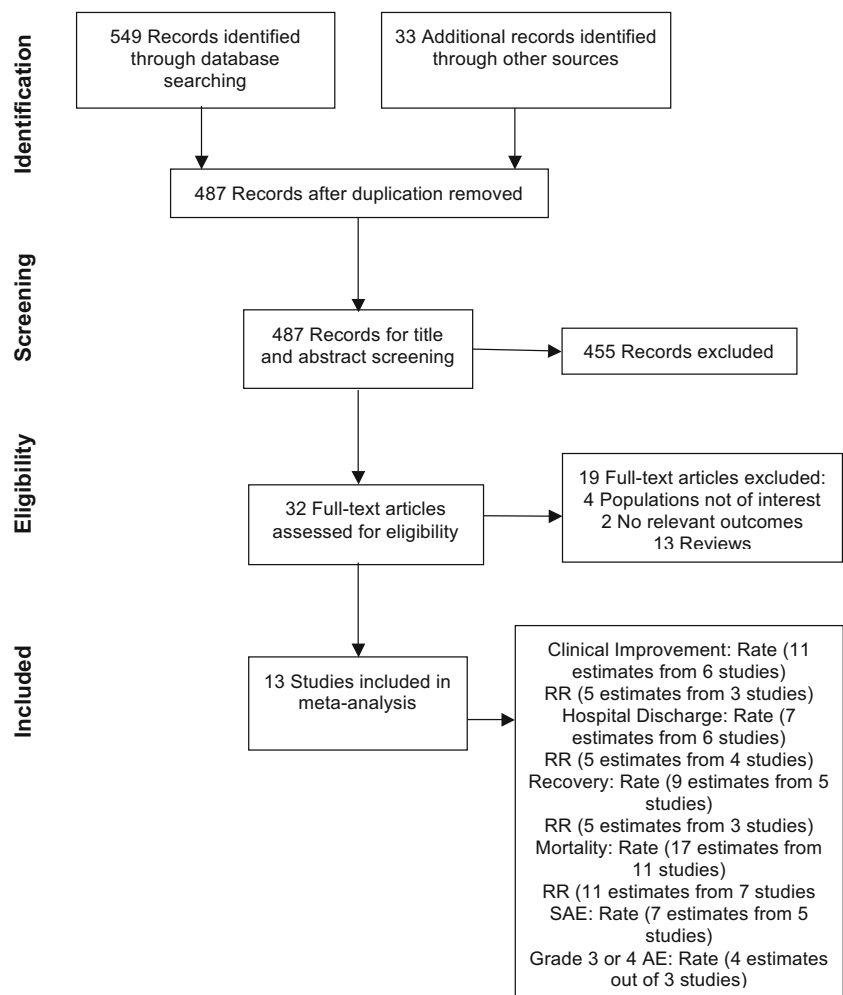Q statistic and I^2 statistic were used to assess heterogeneity across eligible studies. As the Q statistic is underpowered to detect true heterogeneity with a limited number of eligible studies. We used a 10% significance level for the Q statistics to increase the power to detect heterogeneity among the 13 eligible studies. Lastly, funnel plots, the Egger test, and the trim and fill analysis were used to detect publication bias. All statistical analyses were performed in Stata 16.0 (Stata Corporation, College Station, TX) by JT.

Results

Results of Literature Search

Figure 1 shows the process of our study selection. The initial searches in six individual electronic databases yielded 549 records, of which 95 were duplicates, leaving 487 records for title and abstract screening. Thirty-two publications were identified for full-text screening. Among these publication, 13 studies assessed the treatment effect of remdesivir among hospitalized COVID-19 patients and were included in our meta-

Fig. 1 The process of the study selection

549 Records identified through database searching

33 Additional records identified through other sources

487 Records after duplication removed

487 Records for title and abstract screening

455 Records excluded

32 Full-text articles assessed for eligibility

19 Full-text articles excluded:
4 Populations not of interest
2 No relevant outcomes
13 Reviews

13 Studies included in meta-analysis

Clinical Improvement: Rate (11 estimates from 6 studies)
RR (5 estimates from 3 studies)
Hospital Discharge: Rate (7 estimates from 6 studies)
RR (5 estimates from 4 studies)
Recovery: Rate (9 estimates from 5 studies)
RR (5 estimates from 3 studies)
Mortality: Rate (17 estimates from 11 studies)
RR (11 estimates from 7 studies
SAE: Rate (7 estimates from 5 studies)
Grade 3 or 4 AE: Rate (4 estimates out of 3 studies)

Identification / Screening / Eligibility / Included

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analysis. There were six RCTs, three cohort studies, three single-arm prospective studies, and one chart review.

Description of Studies

Table 1 describes the characteristics of studies included in this meta-analysis. Overall, we identified 5068 COVID-19 patients who received remdesivir and 4934 COVID-19 patients who served as controls during their hospital stay within the 13 eligible studies [16–28]. Of the 10,002 COVID-19 patients in this analysis, 70.7% were male. Most patients were over 55 years old. All participants were hospitalized due to COVID-19 and, for 11 of 13 eligible studies, all participants fell within one of the following categories: (1) had an oxygen saturation (SaO2/SPO2) of 94% or less while breathing ambient air, (2) needed supplemental oxygen, (3) needed mechanical ventilation. Among the two additional studies, one excluded patients on mechanical ventilation and extracorporeal membrane oxygenation (ECMO) [22], while the other enrolled patients with a SaO2/SPO2 > 94% [19]. Although the study by Goldman et al. was an RCT, they did not incorporate a control group. Consequently, we treated this study as a prospective cohort study. In Kalil et al.'s study, the group of COVID-19 patients who solely received remdesivir was extracted, and the study was treated as a single-arm prospective cohort study [27].

Assessment of Risk Bias

Table 2 presents the risk bias of eligible studies. RCT studies had a low risk of selection bias, as these studies all provided detailed information about randomization [17–19, 22, 25, 27]. The rest of included studies were either single-arm prospective studies, chart reviews, or cohort studies. Randomization and group allocation were not part of these study designs. We put "Not applicable" to these studies. Three studies used double-blinded study designs [17, 18, 27], and were assessed as "low-risk" for detection bias. We assigned "Not applicable" to the rest of studies due to the unblinded study design. A "low-risk" were assigned to all studies, except for Lee et al's study [21]. Lee et al extracted data from electronic medical records and did not report detail information about incomplete outcomes. Hence, we put an "unknown risk" for this study. For reporting bias, a "low-risk" was assigned to RCT studies [17–19, 22, 25, 27]. All these RCT studies provided detailed results of outcomes of interests in supplementary. Other studies were assigned an "unknown risk" due to the lack of data to assess the potential reporting bias.

Effect of Remdesivir on Mortality

The mortality rate at 28 ± 2 days of hospitalized patients on remdesivir varied from 1 to 56% in 17 estimates from 10 studies (Fig. 2a). Several studies contributed two estimates

of mortality, as heterogeneous effects were observed across different study populations (non-mechanical ventilated vs. mechanically ventilated patients) and varied regimens (5 vs. 10 days course). The pooled mortality rate was 15% (95% CI: 9%, 22%) among patients on remdesivir. When stratified by ventilation status, a 29% (95% CI: 19%, 39%) mortality rate was observed among mechanically ventilated patients, and a 6% (95% CI: 3%, 9%) mortality rate was observed among those without mechanical ventilation (P < 0.001). Seven studies had a control group and reported the number of deaths in each group. The pooled RR of remdesivir on mortality was 0.83 (95% CI: 0.65, 1.06) (Fig. 2b), suggesting that patients on remdesivir were 17% less likely to die when compared to COVID-19 patients in the control group.

When stratified by ventilation status, mechanically ventilated patients were 16% (RR: 0.84, 95% CI: 0.52, 1.35) less likely to die, while non-ventilated patients were 20% (RR: 0.80, 95% CI: 0.62, 1.03) less likely to die at 28 ± 2 days. No significant differences between mechanical and non-mechanical groups were observed (P = 0.98). The Q statistic rejected the null hypothesis that true heterogeneity was due to chance (chi-square: 20.05, degree of freedom = 9, P = 0.02) at a 10% significance level. The I^2 statistic indicated that 60.2% of the variance could be explained by true heterogeneity.

Effect of Remdesivir on Clinical Improvement

In this meta-analysis, six studies reported 11 estimates of clinical improvement at either 14 ± 1 or 28 days among hospitalized patients on remdesivir (Fig. 3a). The clinical improvement rates varied from 16 to 89%. The overall pooled clinical improvement rate was 64% (95% CI: 51%, 78%). When stratified by period, the pooled clinical improvement rates at day 14 ± 1 and 28 ± 1 were 52% (95% CI: 35%, 69%) and 79% (95% CI: 66%, 93%), respectively. In the mechanical ventilated group, the clinical improvement rate was 36% (95% CI: 0.14, 0.58). A higher clinical improvement rate of 74% (95% CI: 65%, 84%) was observed in the non-mechanical ventilated group. The overall pooled RR of remdesivir on clinical improvement was 1.12 (95% CI 1.05, 1.19) among three studies having a control group (Fig 3b.). Only one study reported clinical improvement in the mechanical ventilated group. Among the non-mechanical ventilated group, patients on remdesivir were 12% (RR 1.12, 95% CI 1.05, 1.19) more likely to achieve clinical improvement than those in the control group. As the Q statistic was 4.13 (P = 0.39, degree of freedom 4), the true heterogeneity may be due to chance. The true heterogeneity could explain 23.7% of the variance.

Effect of Remdesivir on Recovery

Five studies contributed nine recovery rates at either 14 ± 1 or 28 days with a range of 37% to 93% among hospitalized

Table 1 Description of the characteristics of eligible studies

Study	Design	Location	Intervention	Control	Sample size		Gender (% male)	Age	Outcomes
					Treatment (n)	Control (n)			
Beigel et al. 2020 [17]	RCT	-North America -Europe -Asia	Remdesivir 200 mg day 1 100 mg day 2–10	Saline	541	521	64.4	58.9 (15)*	-Recovery -Mortality -SAE -Discharge
Wang et al. 2020 [18]	RCT	-China	Remdesivir 200 mg day 1 100 mg day 2–10	Placebo Infusions	158	78	59.3	65 (56–71)**	-Clinical Improvement -Mortality -SAE -Discharge
Goldman et al. 2020 [22]	RCT	-USA -Europe -Asia	Remdesivir 200 mg day 1 100 mg day 2–5	Remdesivir 10 day Regimen	197	200	63.7	61 (50–69)**	-Clinical Improvement -Mortality -SAE -Discharge
Pan et al. 2020 [25]	RCT	-Europe -Canada -Latin America -Asia -Africa	Remdesivir 200 mg day 1 100 mg day 2–10	Standard of Care	2743	2708	76	.	-Mortality
Spinner et al. 2020 [19]	RCT	-Europe -USA -Asia	Remdesivir 200 mg day 1 100 mg day 2–5	Standard of Care	191	200	61.1	58 (48–66)**	-Recovery -Clinical Improvement -Mortality -SAE -Discharge
Grein et al. 2020 [16]	Single-arm Prospective Study	-Europe -Canada, -US -Japan	Remdesivir 200 mg day 1 100 mg day 2–10	.	53	.	75	64 (48–71)**	-Mortality -Clinical Improvement -SAE
Antinori et al. 2020 [26]	Single-arm Prospective Study	-Italy	Remdesivir 200 mg day 1 100 mg day 2–10	.	35	.	74.3	63 (51–69)**	-Mortality -Discharge
Pasquini et al. 2020 [23]	Cohort	-Italy	Remdesivir 200 mg day 1 100 mg day 2–10	Standard of Care	25	26	92.2	67 (59–75.5)**	-Mortality
Lee et al. 2020 [21]	Chart Review	-USA	Remdesivir 200 mg day 1 100 mg day 2–5	.	76	.	47.4	63 (1.62)*	-Mortality
Kalil et al. 2020 [27]	RCT (Control Arm)	-USA -Singapore -Asia -Latin America -Europe	Remdesivir 200 mg day 1 100 mg day 2–10	.	518	.	64.3	55.8 (16)*	-Mortality -Recovery
Lapadula et al. 2020 [24]	Cohort	-Italy	Remdesivir	Standard of Care	33	80	79.6	61 (56–67)**	-Mortality

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Table 1 (continued)

Study	Design	Location	Intervention	Control	Sample size		Gender (% male)	Age	Outcomes
					Treatment (n)	Control (n)			
									-Discharge
Rivera et al. 2020 [20]	Cohort	-USA	Remdesivir 200 mg day 1 100 mg day 2–10	Standard of Care	57	1321	56	68 (58–76)**	-Mortality
Falcão et al. 2021 [28]	Single-arm Prospective Study	-Portugal	Remdesivir 200 mg day 1 100 mg day 2-10, or, 100 mg day 2–5	.	48	.	62	62 (17)*	-SAE

Interventions for all studies consisted of treatment with remdesivir with administration of 200 mg on the first day of treatment followed by either 5 or 10 days of treatment with 100 mg. This treatment regimen corresponded with recommended treatment administration by the National Health Department

SAE, severe adverse effect; *RCT*, randomized controlled trial; *USA*, United States of America

*mean (standard deviation)

**median (interquartile range)

patients receiving remdesivir treatment (Fig. 4a). The overall recovery rate was 70% (95% CI: 57%, 83%). When stratified by period, the pooled recovery rates at day 14 ± 1 and 28 ± 1 were 60% (95% CI: 41%, 79%) and 77% (95% CI: 61%, 93%), respectively. In the non-mechanical ventilated group, 77% (95% CI: 57%, 83%) of patients on remdesivir were recovered during the study period, while 43% (95% CI: 33%, 54%) of patients were recovered in the mechanical ventilated group. Three studies reported five estimates of RR of remdesivir on recovery. The pooled RR was 1.09 (95% CI 1.04, 1.13) (Fig. 4b). Only one study reported a recovery rate among mechanically ventilated patients [18]. Non-mechanically ventilated patients receiving remdesivir were 9% (95% CI 1.04, 1.13) more likely to achieve recovery than their counterparts without remdesivir. The Q statistic indicates the true heterogeneity across studies may be due to chance (chi-square 1.57, degree of freedom 4, $P = 0.81$).

Effect of Remdesivir on Hospital Discharge

There were seven estimates of the hospital discharge rate at 28 days from five studies. These estimates ranged from 33 to 90% among COVID-19 patients on remdesivir treatment (Fig. 5a). The pooled hospital discharge rate was 74% (95% CI: 60%, 87%). The hospital discharge rates were 60% (95% CI: 9%, 100%) and 81% (95% CI: 67%, 95%) in mechanical and non-mechanically ventilated groups, respectively. The pooled RR of remdesivir on hospital discharge based on five RRs from four studies was 1.12 (95% CI 1.06, 1.19) (Fig. 5b). From results reported by Lapadula *et al.*, mechanically ventilated COVID-19 patients on remdesivir were 39% (RR 1.39, 95% CI 1.10, 1.74) more likely to be discharged than their counterparts on the standard of care [24]. The synthesized RR among non-mechanical ventilated patients was 1.08 (95% CI 1.06, 1.19). The true heterogeneity across studies could be due to chance (chi-square 6.50, degree of freedom = 4, $P = 0.16$) at a 10% significance level. The true heterogeneity could explain 26.4% of the variance.

SAE and Grade 3 or 4 AE Among COVID-19 Patients on Remdesivir

Seven estimates of SAE rates from five studies (Fig. 6a) and four estimates of Grade 3 or 4 AE from three studies (Fig. 6b) were found. The pooled SAE rate and Grade 3 or 4 rate were 21% (95% CI: 13%, 29%) and 30% (95% CI: 12%, 48%), respectively. Mechanically ventilated COVID-19 patients on remdesivir were more likely to have an SAE (35%) when compared to non-mechanically ventilated patients (20%) (Fig. 6a). The true heterogeneity across studies for both SAE and Grade 3 or 4 AE were not due to chance, as Q statistics rejected the null hypothesis at a 10% significance level.

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Table 2 Summary of risk of bias among eligible studies in this meta-analysis

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Beigel et al. 2020 [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wang et al. 2020 [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Goldman et al.2020 [22]	Low risk	Low risk	NA	NA	Low risk	Low risk
Pan et al. 2020 [25]	Low risk	Low risk	NA	NA	Low risk	Low risk
Spinner et al. 2020 [19]	Low risk	Low risk	NA	NA	Low risk	Low risk
Grein et al. 2020 [16]	NA	NA	NA	NA	Low risk	Unknown risk
Antinori et al. 2020 [26]	NA	NA	NA	NA	Low risk	Unknown risk
Pasquini et al. 2020 [23]	NA	NA	NA	NA	Low risk	Unknown risk
Lee et al. 2020 [21]	NA	NA	NA	NA	Unknown risk	High risk
Kalil et al. 2020 [27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lapadula et al. 2020 [24]	NA	NA	NA	NA	Low risk	Unknown risk
Rivera et al. 2020 [20]	NA	NA	NA	NA	Low risk	Unknown risk
Falcão et al. 2021 [28]	NA	NA	NA	NA	Low risk	Unknown risk

NA not applicable

Publication Bias

For all outcomes of interest, funnel plots of RRs were symmetric (Supplementary Fig 1a-1d) and Egger tests indicated P-values greater than 0.05. The trim and fill test did not trim or fill any studies included within this meta-analysis. As a consequence, we concluded that there was no significant publication bias for RRs of the outcomes of interest.

For rates of mortality, clinical improvement, recovery, hospital discharge, SAE, Grade 3 or 4 AE, funnel plots tended to be symmetric, and several results were out of the pseudo 95% CI (Supplementary Fig 2a-2f). The Egger test of mortality and
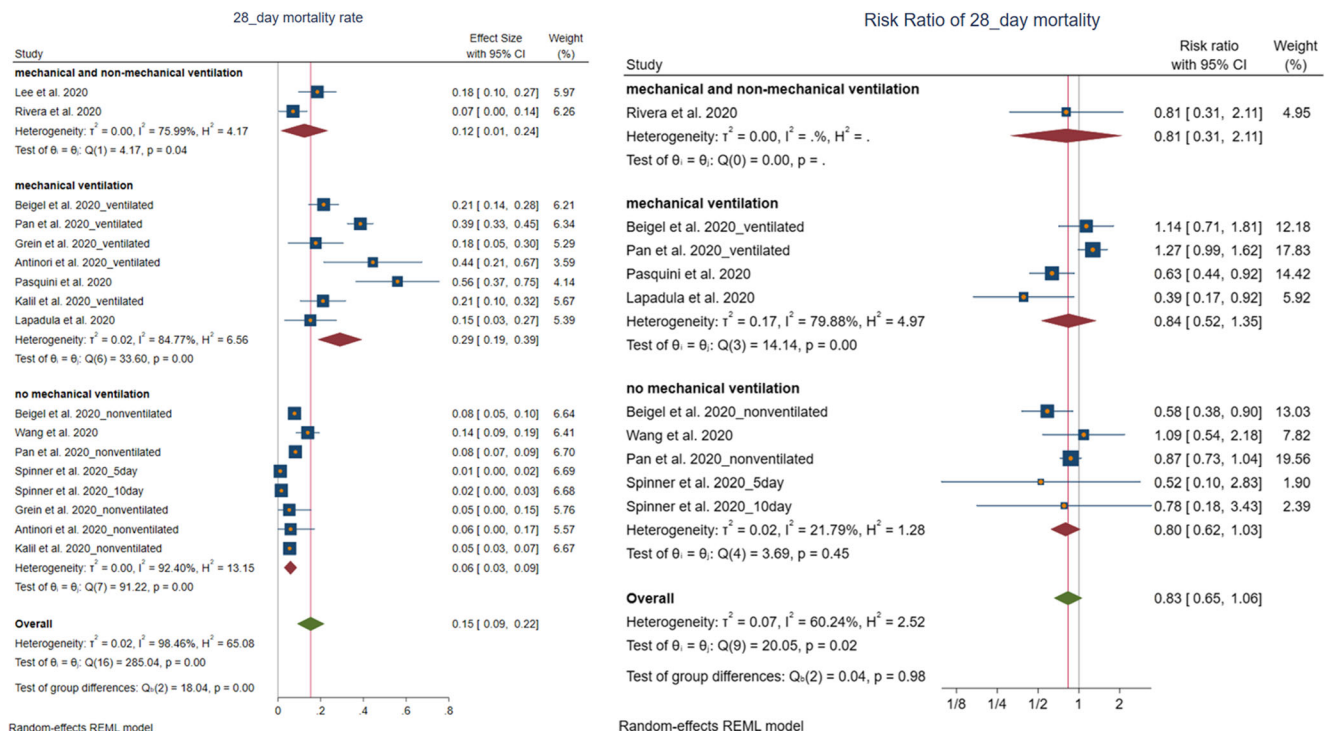

Fig. 2 The 28-day mortality rate of hospitalized patients on remdesivir in 17 estimates from 10 studies
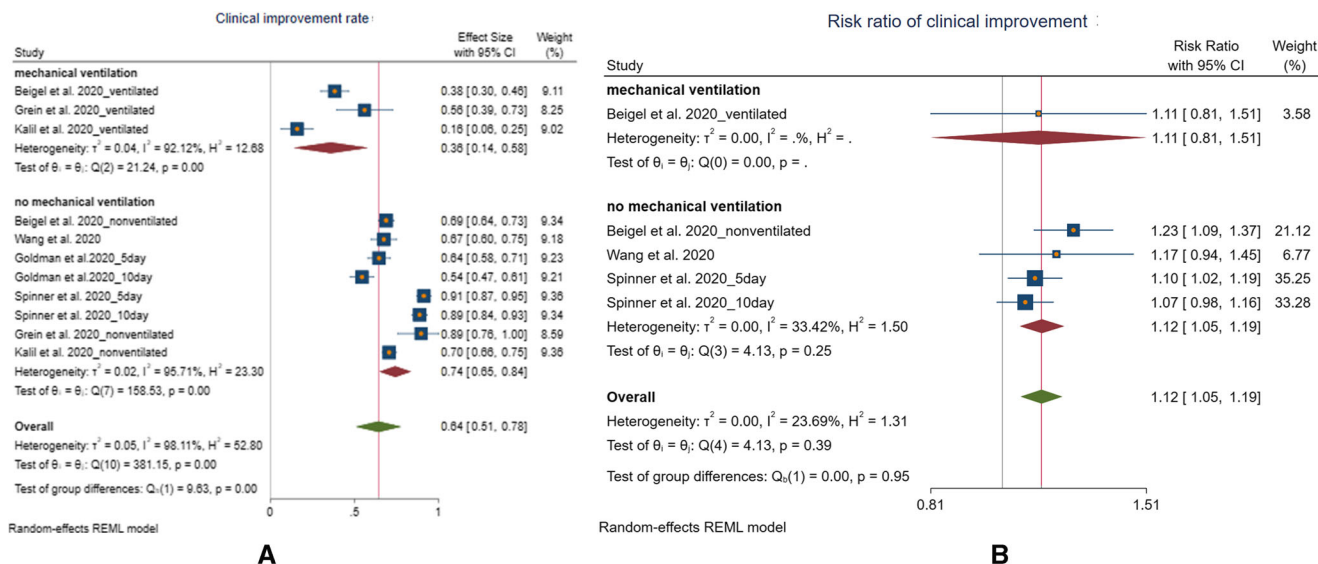
Fig. 3 Six studies reported 11 estimates of clinical improvement among hospitalized patients on remdesivir

recovery rates rejected the null hypothesis that no small study exits (P < 0.05). Thus, although the trim and fill analysis did not yield any trim or fill, publication bias may still exist for mortality and recovery rates. The Egger test of clinical improvement, hospital discharge, SAE, and Grade 3 or 4 AE did not reject the null hypothesis (P > 0.05), and the trim and fill test did not yield any trim or fill for these outcomes. Therefore, publication bias was unlikely to exist for these variables.

Discussion

This study is one of a few meta-analyses to synthesize multiple clinical outcomes (e.g., mortality, clinical improvement,

recovery, and hospital discharge) and safety (SAE and Grade 3 or 4 AE) of remdesivir from varied study designs. From our results, remdesivir was found to have a moderate-favorable effect on hospitalized COVID-19 patients with significant, and favorable effects on clinical improvement, recovery, and hospital discharge. However, we did not detect a significant effect of remdesivir on mortality. Finally, our results suggest that 20–30% of patients on remdesivir may experience an SAE or Grade 3 or 4 AE.

Generally, the administration of remdesivir and the assessment of clinical outcomes were comparable across studies. Because eligible studies predominantly adopted the ordinal score to assess clinical outcomes, assessment of these factors was consistent across studies and the potential influence of
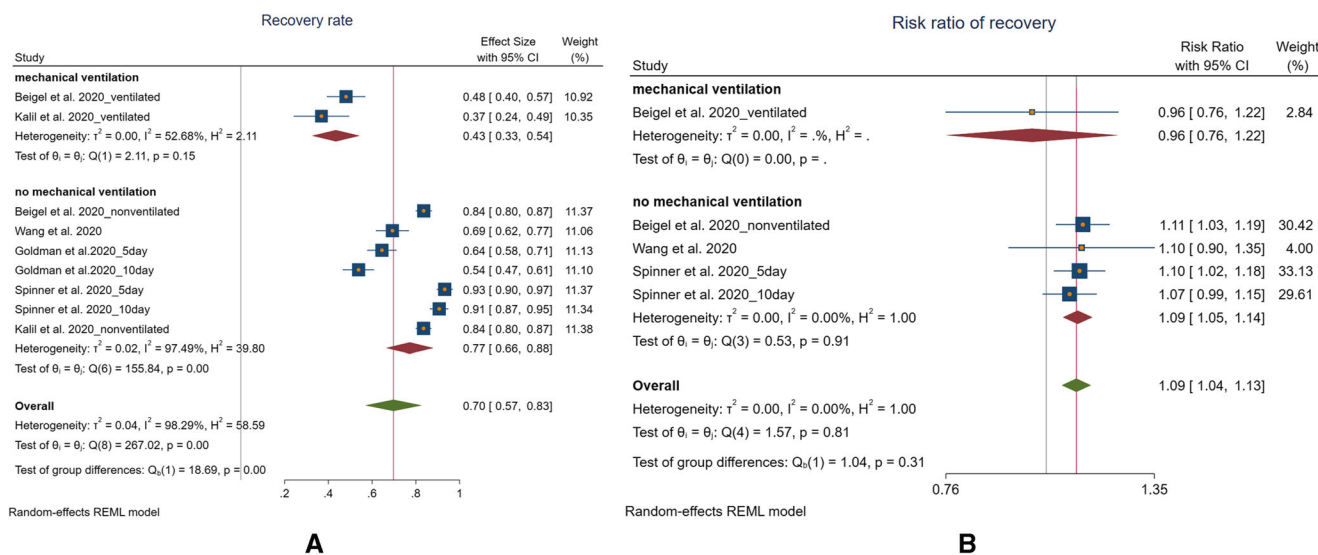
Fig. 4 Five studies contributed nine recovery rates among hospitalized patients receiving remdesivir treatment

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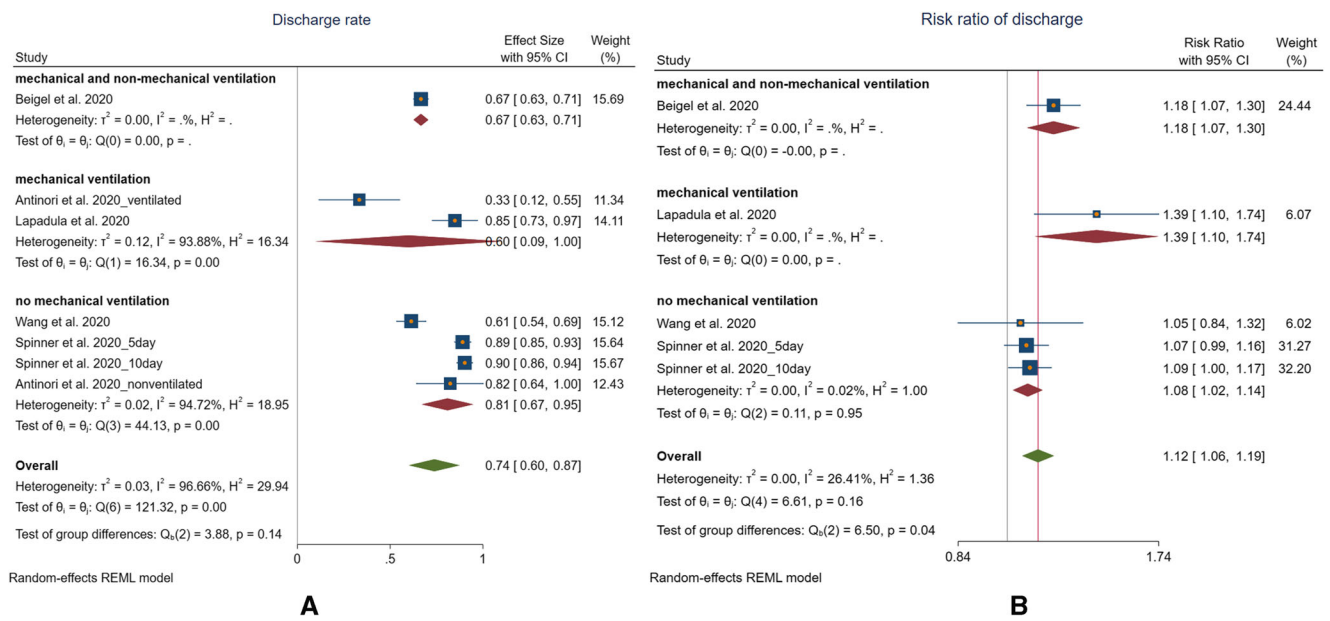
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Fig. 5 Seven estimates of the hospital discharge rate at 28 days from five studies

reporting bias is limited. Additionally, most studies used the recommended 10-day course of remdesivir. Only Goldman *et al.* and Spinner *et al.* included patient groups who received a 5-day course of treatment [19, 22]. Even so, results of interest were not significantly different between different treatment regimens.

Our heterogeneity assessment suggested that the majority of variances among rates of outcomes of interest were attributable to true heterogeneity. This, however, may additionally be caused by the variation in study populations introduced by case severity or study location [16–28]. Although most hospitalized COVID-19 patients were male and in their 50s across

studies, the disease severity varied significantly. Eligible studies could include any combination of ventilated and non-ventilated patients [16–28]. Further, patients with severe clinical status were at higher risk of death and lower risk of clinical improvement, recovery, and hospital discharge, consequently resulting in a trend towards worse clinical outcomes within studies assessing this population. When stratified by ventilation status, results still indicated significant heterogeneity. As previously mentioned, study location is an additional factor that may contribute to this finding as pandemic status, healthcare resources, and treatment guidelines can drastically vary by study location. Several eligible studies included
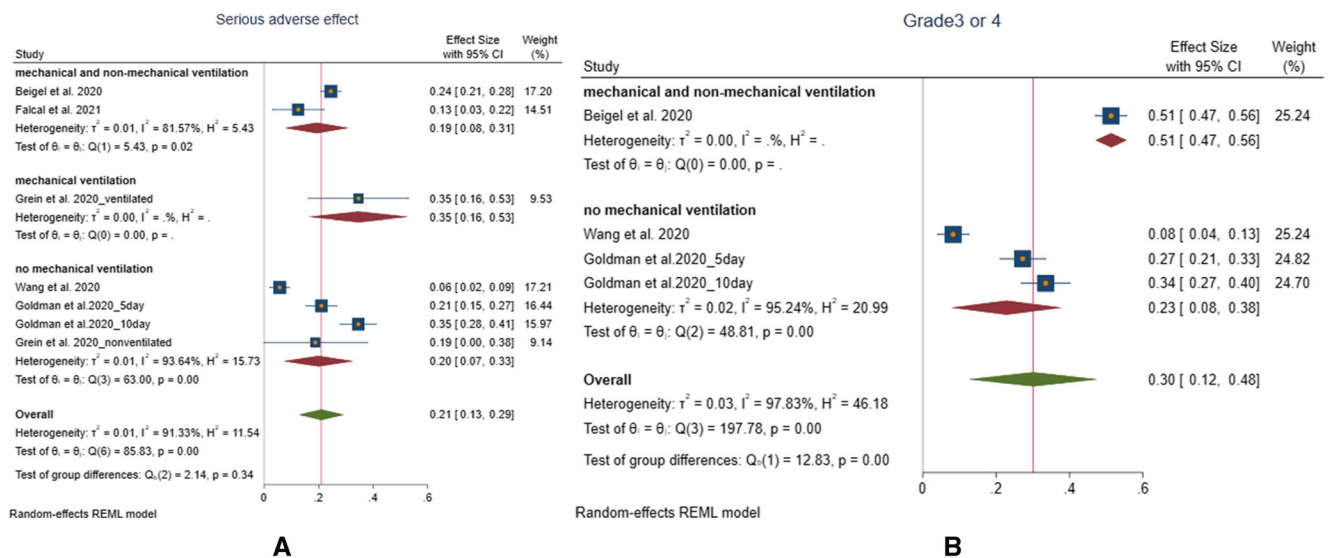

Fig. 6 Seven estimates of SAE rates from five studies and four estimates of Grade 3 or 4 AE from three studies

within the meta-analysis were multi-site research studies spanning multiple countries [16, 17, 19, 22]. Other eligible studies were either single or multi-site studies conducted within the same country [18, 23, 24]. Although significant variance in rates was observed among outcomes of interest in this meta-analysis, the pooled results serve as a valuable summary of clinical outcomes among hospitalized COVID-19 patients worldwide.

When it comes to RRs of clinical outcomes, heterogeneity assessment indicated that the majority of variances of RRs of outcomes of interests were due to chance, except for RR of mortality. The majority of studies reporting RRs were either RCTs or cohort studies, both of which are known to characteristically have more rigorous operational procedures and clinical guidelines. Naturally, RRs serve as a comparison between intervention and control groups and, as a result, are less likely to be influenced by varied population and/or location-specific risk factors. Though we were able to identify four studies assessing RR of mortality among mechanically ventilated patients, two cohort studies in Italy indicated a favorable effect of remdesivir on mortality [23, 24], while the other two studies with multiple study sites suggested a worse survival among ventilated patients on remdesivir [17, 25] As a consequence, more studies are needed to explore remdesivir's effect on mortality among ventilated COVID-19 patients.

Our meta-analysis has a few strengths and limitations. This meta-analysis is a comprehensive assessment of the effect of remdesivir on multiple clinical outcomes (e.g., clinical improvement, hospital discharge, and mortality), while other published meta-analyses only synthesized mortality and/or adverse effect from a few studies [29–32]. In addition, we included cohort studies, chart reviews, and single-arm prospective studies, which could reflect the effectiveness of remdesivir in real-world clinical settings than those only included RCT studies. [29–32] There are several limitations in this study. We observed significant true heterogeneity across studies, even when we stratified by the severe of disease status. This could lead to biased synthesized results. Reporting biases could exist among non-RCT studies, as these studies usually had less restricted protocol of results reporting.

In conclusion, our study serves as a comprehensive meta-analysis to evaluate the effect of remdesivir on multiple clinical outcomes among hospitalized COVID-19 patients. Our results suggest that remdesivir has a moderate-favorable effect on mortality, clinical improvement, recovery, and hospital discharge among non-mechanically ventilated patients as opposed to mechanically ventilated patients. Overall, results from the meta-analysis suggest that remdesivir is beneficial for hospitalized COVID-19 patients and may be potentially impactful as a treatment strategy in non-mechanically ventilated patient populations.

Declarations

Appendix

The search strategy for PubMed is listed below:

(1) Remdesivir strings: (Remdesivir [Supplementary Concept] OR GS-5734 OR "GS 5734" OR "GS-441524 triphosphate")

(2) Coronavirus strings: (COVID-19 [Supplementary Concept] OR SARS-CoV-2 [Supplementary Concept] AND "2019 novel coronavirus disease" OR "COVID-19 pandemic" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "2019 novel coronavirus infection" OR "2019-nCoV infection" OR "coronavirus disease 2019" OR "severe

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acute respiratory coronavirus syndrome 2" OR "coronavirus disease-19" OR "2019-nCoV disease" OR "COVID-19 virus infection")

(3) Published year: ("2019"[PDAT] : "2020"[PDAT])

(4) The strategy was 1&2&3

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