ORIGINAL ARTICLE

Among Patients with COVID-19, should Remdesivir be Used for Treatment? A Systematic Review and Meta-analysis

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ABSTRACT

Background. Remdesivir is an intravenously administered antiviral drug that inhibits RNA-dependent RNA polymerase. In vitro studies have shown that remdesivir can inhibit the growth of the COVID-19 virus in infected Vero cells and can inhibit infection in human cell lines.

Objective. To determine the efficacy and safety of remdesivir in treating patients with COVID-19 infection.

Methods. A systematic search of electronic medical literature databases was done from inception until September 4, 2022. Search for ongoing studies and preprints was also done. Risk of bias assessment was done using Cochrane risk of bias tool version 2.0. Measures of effect used were relative risk (RR) and 95% confidence interval (CI). Subgroup analysis by disease severity was preplanned. The estimates for efficacy and safety of remdesivir was calculated using Review Manager 5.4 software.

Results. Nine randomized controlled trials with 13,085 participants were identified. Eight of the included studies recruited confirmed COVID-19 patients needing hospitalization, while one study limited recruitment to non-hospitalized patients. Remdesivir showed significant benefit for outpatients with mild to moderate disease with at least one risk factor for disease progression in terms of COVID 19-related hospitalization (RR 0.13 95% CI 0.03 to 0.59), all-cause hospitalization (RR 0.28, 95% CI 0.10 to 0.75), and need for medically-attended visits (RR 0.19, 95% CI 0.07 to 0.56). For hospitalized patients, remdesivir had a slight benefit in reducing all-cause mortality at day 28 (RR 0.90, 95% CI 0.83 to 0.98). Subgroup analysis by disease severity showed a trend towards reduction in mortality among those with severe disease (RR 0.61, 95% CI 0.35 to 1.07), with no effect on those with critical disease (RR 0.96, 95% CI 0.87 to 1.04), and inconclusive effect for those with mild-moderate disease (RR 0.74, 95% CI 0.49 to 1.11). Remdesivir showed benefit in decreasing clinical deterioration (RR 0.75, 95% CI 0.61 to 0.89), improving recovery rate (RR 1.07, 95% CI 1.01 to 1.13), and reducing the need for mechanical ventilation (RR 0.68, 95% CI 0.51 to 0.90). There was inconclusive effect on the need for ICU admission (RR 0.98, 95% CI 0.43 to 2.22). No increased risk of adverse events (RR 0.98, 95% CI 0.91 to 1.06), including serious adverse events (RR 0.77, 95% CI 0.57 to 1.03), was seen.

Discussion. Based on the available evidence, remdesivir shows benefit in the treatment for patients with mild, moderate, and severe COVID-19 infection. However, there was no benefit in mortality noted among those with critical disease requiring mechanical ventilation. Remdesivir demonstrated a good safety profile, with no increased risk of adverse events compared to control. These results are consistent with the international agencies' recommendations for the use of remdesivir among patients with mild, moderate or severe COVID-19 infection, but not for those with critical infection.

Conclusion. Current evidence supports the use of remdesivir as treatment for selected patients with COVID-19.

Keywords: COVID-19, remdesivir, mortality

eISSN 2094-9278 (Online)
Published: August 15, 2024
https://doi.org/10.47895/amp.vi0.7288

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INTRODUCTION

Remdesivir is an intravenously administered antiviral drug originally developed for the Ebola virus that is currently being evaluated as a potential treatment for COVID-19. It is a nucleotide analogue that inhibits RNA-dependent RNA polymerase.[1] In vitro studies and studies in animal models have demonstrated its antiviral activities against an array of RNA viruses (e.g., MERS-CoV, Ebola, and SARS-CoV).[2-4] An in vitro study has shown that remdesivir can inhibit the growth of the COVID-19 virus in infected Vero cells and can inhibit infection in human cell lines.[5]

There are several clinical studies that evaluate the effect of remdesivir on the treatment of COVID-19. The objective of this systematic review and meta-analysis is to determine the effectiveness and safety of remdesivir for the treatment of patients with COVID-19. This review synthesizes all available evidence on the use of remdesivir for COVID-19, and provides an evidence base to support the creation of recommendations in the Philippine COVID-19 clinical practice guidelines.

METHODS

This review is an update of the previously completed review. A systematic search was done until September 4, 2022 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and remdesivir. We also looked at the COVID-Network Meta-Analysis (COVID-NMA) Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. The full search strategy is shown in Appendix 1. Unpublished studies were searched by searching for pharmaceutical reports and reports from government agencies such as the Food and Drug Administration and the Department of Health. Only randomized controlled trials (RCTs) that compared remdesivir against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, and adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of remdesivir. Analysis was separated for hospitalized and non-hospitalized patients to facilitate the creation of clinically relevant recommendations. For studies that reported aggregate data on overlapping subgroup categories, the data was placed in the more severe subgroup/higher level of oxygen requirement subgroup.

Articles were selected based on the following inclusion criteria:

- **Population:** Patients with COVID-19 of any age, with any co-morbidities, any severity
- **Intervention:** Remdesivir
- **Comparator:** placebo, standard care
- **Outcomes:** mortality, clinical deterioration or improvement, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, adverse events
- **Study designs:** randomized controlled trials

All articles that fulfilled the inclusion criteria from inception until September 4, 2022 were retrieved. Observational studies and quasi-randomized trials were excluded. Two authors independently performed the search, screening of titles and abstracts, and selection of articles for inclusion in the study. The same two authors independently assessed risk of bias using Cochrane risk of bias tool version 1.0 and extracted the data from each study. Disagreements were resolved by discussion among the two authors until consensus was reached.

The estimates for efficacy and safety of remdesivir were calculated using Review Manager (RevMan) 5.4 software. The effect measure used for the efficacy and safety outcomes was relative risk (RR) with its corresponding 95% confidence interval (CI). The outcome of time to clinical recovery was reported as hazard ratio (HR) with 95% CI. In case of missing data, study authors were contacted for the needed data. COVID-NMA Living Data was also used to check if the data was available there, since the authors of the COVID-NMA Living Data contact the relevant study authors in case of missing data. In case data was still missing despite these efforts, no imputation was done. These data were excluded from the analysis.

Forest plots were generated using RevMan 5.4 software using the random effects model. Heterogeneity was quantified using chi-square tests and the inconsistency statistic (I2). Studies with $I^2 > 50\%$ and $p < 0.10$ were considered to have significant heterogeneity. Subgroup analysis was done to explore the source of heterogeneity. Subgroup analysis by disease severity, level of oxygen requirement, and treatment duration was planned. Sensitivity analysis excluding studies with high risk of bias, and using an alternative classification of studies with overlapping subgroup categories as an alternative meta-analysis model were done.

Publication bias was to be assessed using visualization of funnel plots if there were at least 10 included studies. Worst-case sensitivity analysis to account for reporting bias was to be done if significant missing results were observed in the results, in order to assess for the potential risk of bias of these missing results.

Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

RESULTS

Search Results

A total of 488 articles were identified through database search and manual search. There were 481 records excluded after removal of duplicates and screening of abstracts because they did not match the selection criteria or the type of population, intervention, comparison, and outcome (PICO) specified for this review. The full-text reports of the remaining seven studies were retrieved and assessed for eligibility. Five studies were excluded—1 study was not randomized, and 4 studies reported outcomes that are not part of the prespecified PICO. Two studies were included in the update. Search of trial registries showed 149 trials. After removal of duplicates and screening the trial data, 116 trials were excluded, leaving 33 ongoing trials identified for this review. The search flow diagram is shown in Figure 1.

Characteristics of Included Studies

Nine RCTs involving a total of 13,085 study participants evaluated the use of remdesivir as treatment for patients with COVID-19.[6-14]

Eight of the included studies recruited confirmed COVID-19 patients needing hospitalization, while one study[13] limited recruitment to non-hospitalized patients. The severity of disease of the study participants were mild to critical in four studies, mild to moderate in two studies, mild to severe in one study, moderate to severe in one study, severe in one study and unclear in one study.

All studies involved adult patients. The study on non-hospitalized patients included study participants 12 years old and above, but only 8 participants belonged to the 12 to 18-year-old age group.[13] There were no RCTs involving only children. The median duration of symptoms before randomization and treatment initiation ranged from 8 to 10 days in five studies[6,8,9,11,14]; while one study reported a 7-day mean duration of symptoms before hospital admission.[12] Only one study reported recruiting patients within 7 days of symptom onset.[13] Studies were mostly conducted in high and upper-middle income countries. Seven RCTs used a 10-day course of remdesivir [6-9,11,12,14], two studies used a 5-day course[10,11], and the study in outpatients used a 3-day course[13]. Remdesivir was compared to placebo in 1 study,[13] while the rest compared remdesivir to the local standard of care.[6-12,14] Standard of care allowed the use of corticosteroids in seven of the studies.[6,7,9-12,14] Other potential COVID-19 treatments were being investigated in parallel to remdesivir in two multi-arm trials.[7,12]

The primary outcome in all studies was all-cause mortality, with duration of follow-up ranging from 24 to 90 days.[6-14] Clinical status or improvement was reported by all studies, using variable 6- 8- or 10- point scales. The outcomes of five studies with sufficient description of this outcome measure were converted to the WHO ordinal scale for pooled analysis.[6,8-11] Other outcomes reported were time to clinical improvement or recovery [5,8,9,11], need for ICU admission[12], need for mechanical ventilation[7-9,11,12,14], adverse events[6,8,9,11,13,14], and serious adverse events[6,8,9,11,13,14]. Characteristics of included studies are summarized in Appendix 2.

The overall certainty of evidence was low due to serious risk of bias and inconsistency or imprecision in several critical outcomes. The serious risk of bias was due to concerns in selection, performance bias, detection bias, attrition bias, and reporting bias in most of the included studies.

The risk of bias summary is in Appendix 3. Three studies had over-all low risk of bias, five studies had overall

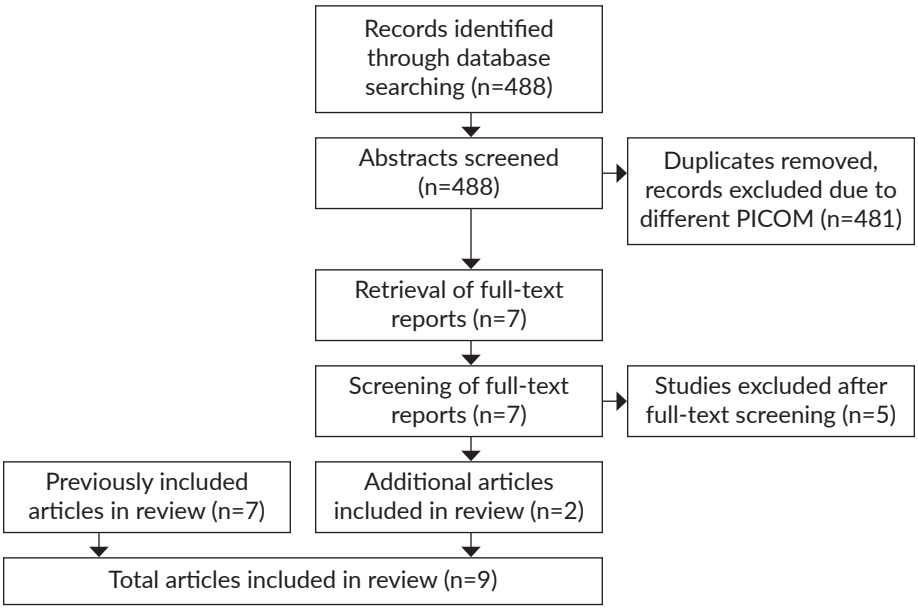

Figure 1. Search flow diagram.

some concerns for bias, and one study had overall high risk of bias. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile is in Appendix 4.

Efficacy Outcomes for Hospitalized Patients

Mortality

Among hospitalized patients, pooled results from eight RCTs (N=12,439) showed that remdesivir had slight benefit on all-cause mortality at day 28 (RR 0.90, 95% CI 0.83 to 0.98; I^2=0%). Sensitivity analysis excluding the studies with very serious risk of bias showed similar results (RR 0.90, 95% CI 0.82 to 0.98; I^2=0%).

Subgroup analysis: Disease severity

Subgroup analysis by disease severity at baseline showed no significant benefit among patients with mild-moderate disease (RR 0.74, 95% CI 0.49 to 1.11; I2=0%). There was a trend towards benefit in reducing mortality among patients with severe disease (RR 0.61, 95% CI 0.35 to 1.07); however, there was significant heterogeneity (I^2=61%). There was no significant difference in mortality among patients with critical disease (RR 0.96, 95% CI 0.87 to 1.04; I^2=0%).

A sensitivity analysis was done where patients on low/high flow oxygen from the WHO Solidarity Trial were included in the severe subgroup instead of the critical subgroup. Results similarly showed no significant benefit among patients with mild-moderate disease (RR 0.74, 95% CI 0.49 to 1.11; I^2=0%), and a trend towards benefit in reducing mortality among patients with severe disease (RR 0.72, 95% CI 0.50 to 1.03); however, there was significant heterogeneity for the severe disease subgroup (I^2=67%). There was no significant difference in mortality in the critical disease subgroup (RR 1.03, 95% CI 0.90 to 1.18; I^2=0%).

Subgroup analysis: Oxygen requirement

Subgroup analysis by oxygen requirement at baseline showed no significant benefit among patients without oxygen requirement (RR 0.74, 95% CI 0.49 to 1.11; I^2=0%). There was a trend towards benefit in reducing mortality among patients on low flow oxygen (RR 0.61, 95% CI 0.35 to 1.07, I^2=61%) and on high flow oxygen (RR 0.90, 95% CI 0.80 to 1.00 I^2=0%). Results on low flow oxygen showed significant heterogeneity. There was a trend towards harm for those on mechanical ventilation (RR 1.06, 95% CI 0.92 to 1.23; I^2=0%). However, the wide confidence interval in all subgroups precluded definite conclusions to be made.

Subgroup analysis: Treatment duration

Subgroup analysis by treatment duration showed inconclusive effect on mortality for those given a 5-day course of remdesivir (RR 0.98, 95% CI 0.37 to 2.56; I^2=0%). There was a slight benefit on mortality among those given a 10-day course (RR 0.90, 95% CI 0.83 to 0.98; I^2=0%).

Other Outcomes

Four RCTs contributed data for clinical improvement. Pooled analysis showed that remdesivir has marginal benefit on clinical improvement up to day 28 (RR 1.07, 95% CI 1.01 to 1.13; I^2=0%). Remdesivir may decrease clinical deterioration as measured by the WHO progression scale (RR 0.75, 95% CI 0.61 to 0.89; I^2=0%). However, no significant effect was seen on time to clinical improvement (HR 1.07, 95% CI 0.91 to 1.25; I^2=50%), with moderate heterogeneity.

Remdesivir has a small benefit in recovery rate (RR 1.22, 95% CI 1.11 to 1.35, I^2=0%). On subgroup analysis according to baseline oxygen requirement, there was significant benefit in recovery rate among patients with severe COVID-19 requiring low flow oxygen support (RR 1.45, 95% CI 1.18 to 1.79). There was no significant benefit for patients not receiving oxygen support (RR 1.16, 95% CI 0.96 to 1.38), those on high flow oxygen or non-invasive mechanical ventilation (RR 1.09, 95% CI 0.76 to 1.57), and on mechanical ventilation or ECMO (RR 0.98, 95% CI 0.70 to 1.37).

There was significant reduction in the need for mechanical ventilation among patients given remdesivir (RR 0.68, 95% CI 0.51 to 0.90); however, there was significant heterogeneity (I^2=81%). There was inconclusive effect in the need for ICU admission (RR 0.98, 95% CI 0.43 to 2.22; 1 RCT, 181 participants).

Efficacy Outcomes for Non-hospitalized Patients

Among non-hospitalized patients, one RCT (N=562) showed that a 3-day course of remdesivir within 7 days of symptom onset reduced risk of COVID-19 related hospitalization (RR 0.13, 95% CI 0.03 to 0.59), all cause-hospitalization (RR 0.28, 95% CI 0.10 to 0.75), and COVID-related medically attended visit (RR 0.19, 95% CI 0.07 to 0.56) by day 28 compared to placebo. Alleviation of symptoms by day 14 was inconclusive (RR 1.41, 95% CI 0.73 to 2.69). None of the patients in both groups died by day 28.

Safety Outcomes

A total of five RCTs (N=4,033) contributed data to the pooled analysis on adverse events among hospitalized patients. Compared to control, patients given remdesivir had no difference in their risk for adverse events (RR 0.99, 95% CI 0.92 to 1.08; I2=31%). There was no significant benefit on serious adverse events (RR 0.84, 95% CI 0.65 to 1.09; I^2=62%).

Among outpatients (1 RCT, N=562), there was no significant difference in adverse events between groups (RR 0.90, 95% CI 0.75 to 1.09). However, there was a reduced risk of serious adverse events in the remdesivir group (RR 0.26, 95% CI 0.10 to 0.70).

Common adverse events were pyrexia, rash, anemia, decreased lymphocyte count, increased neutrophil count, hyperglycemia, increased creatinine level, hypoalbuminemia, and decreased glomerular filtration rate. Other adverse events reported include hypersensitivity reactions (angioedema,

rash), seizures, and elevations in hepatic enzymes. Serious adverse events reported in both groups were respiratory failure, cardiopulmonary failure, and renal failure necessitating renal replacement therapy.

Worst-case sensitivity analysis to account for reporting bias was no longer done given the available results extracted from the studies. Appendix 5 contains the forest plots for the efficacy and safety outcomes.

Recommendations from other Guidelines

The recommendations of other groups[15-18] are summarized in Table 1.

Ongoing studies

There are 33 registered trials on remdesivir. These upcoming and ongoing trials include trials among adolescents, children, pregnant women, outpatients, and patients with chronic kidney disease (Appendix 6).

Table 1. Summary of Recommendations from other Groups

Regulatory Agency	Recommendation
World Health Organization (WHO) (as of September 16, 2022)[15]	We suggest treatment with remdesivir for patients with non-severe COVID-19 at highest risk of hospitalization (conditional recommendation) We suggest treatment with remdesivir for patients with severe COVID-19 (conditional recommendation) We suggest not to use remdesivir for patients with critical COVID-19 (conditional recommendation against)
Infectious Diseases Society of America (IDSA) (as of August 30, 2022)[16]	Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests remdesivir initiated within seven days of symptom onset rather than no remdesivir. (Conditional recommendation, Low certainty of evidence) In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence) In hospitalized patients with severe* COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence) *Severe illness is defined as patients with SpO_2 ≤94% on room air Suggest against the routine initiation of remdesivir in patients on invasive ventilation and/or ECMO. (Conditional recommendation, Very low certainty of evidence)
US National Institutes of Health (NIH) (as of August 8, 2022)[17]	The Panel recommends using remdesivir for the treatment of COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe disease (Moderate recommendation). For patients with COVID-19 who only require minimal conventional oxygen, the Panel recommends using remdesivir without dexamethasone (Moderate recommendation). For most patients with COVID-19 who require conventional oxygen, the Panel recommends using dexamethasone plus remdesivir (Moderate recommendation). For hospitalized patients who require HFNC oxygen or NIV and have certain medical conditions, the Panel recommends adding remdesivir to 1 of the recommended immunomodulator combinations (Weak recommendation). The Panel recommends against the use of remdesivir without immunomodulators in hospitalized patients who require HFNC oxygen or NIV (Strong recommendation). The Panel recommends remdesivir, with or without dexamethasone, for hospitalized children who have a new or increasing need for conventional oxygen, and recommends remdesivir in combination with dexamethasone for children who require oxygen through a high-flow device or NIV (Moderate recommendation). For children hospitalized for COVID-19 who do not require supplemental oxygen, the Panel recommends remdesivir for children aged 12 to 17 years who are at the highest risk for progression to severe disease. (Weak recommendation). There is insufficient evidence for or against the use of remdesivir in hospitalized children aged 28 days to <12 years and weighing ≥3 kg who do not require supplemental oxygen. Remdesivir, as an alternative to ritonavir-boosted nirmatrelvir, can be considered for children aged ≥12 years who are at the highest risk of progression to severe COVID-19. (Weak recommendation). For non-hospitalized children aged <12 years who are at the highest risk of progression to severe disease and for children who are at intermediate risk of severe disease, there is insufficient evidence to recommend either for or against the routine use of remdesivir for the treatment of COVID-19.

Regulatory Agency	Recommendation
Australian COVID-19 Treatment Guidelines (as of September 19, 2022)[18]	Consider using remdesivir in adults with COVID-19 who require oxygen but do not require invasive or non-invasive ventilation. (Conditional recommendation) Do not start remdesivir in adults hospitalized with COVID-19 who require non-invasive or invasive ventilation. Consider using remdesivir within 7 days of symptom onset in unvaccinated adults with COVID-19 who do not require oxygen and who have one or more risk factors* for disease progression. (Conditional recommendation) *Risk factors for disease progression include the following: • Age ≥60 years • Diabetes • Obesity (BMI ≥ 30 kg/m2) • Chronic kidney disease (any stage) • Cardiovascular or cerebrovascular disease (coronary artery disease, congenital heart disease, heart failure, cardiomyopathy or history of stroke) • Hypertension (systemic or pulmonary) • Chronic liver disease • Chronic lung disease (chronic obstructive pulmonary disease, moderate-severe asthma, cystic or pulmonary fibrosis) • Sickle cell disease • Current cancer • Immunocompromised state In addition to at-risk unvaccinated adults, also consider using remdesivir within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and: are immunocompromised regardless of vaccination status; or who are not up-to-date with vaccination and who are at high risk of severe disease on the basis of age and multiple risk factors. (Consensus recommendation) Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 within 7 days of symptom onset in children and adolescents aged 28 days and over and weighing at least 3 kg who do not require oxygen and are at high risk of deterioration, where other treatments are not available / appropriate. (Consensus recommendation) Consider using remdesivir in eligible children and adolescents who have not received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, those who are immunocompromised regardless of vaccination / previous infection status, or those who are not eligible for vaccination based on age but who are at high risk of disease progression. Do not routinely use remdesivir in children and adolescents who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months unless immunocompromised. (Consensus recommendation)

DISCUSSION

This review included 9 RCTs on the use of remdesivir in treatment of COVID-19. Remdesivir showed significant benefit for outpatients with mild to moderate disease with at least one risk factor for disease progression in terms of COVID 19-related and all-cause hospitalizations, and need for medically-attended visits.

For hospitalized patients, remdesivir had a slight benefit in reducing all-cause mortality at day 28. Subgroup analysis by disease severity showed a trend towards reduction in mortality among those with severe disease, with no effect on those with critical disease and inconclusive effect for those with mild-moderate disease. Subgroup analysis by oxygen requirement showed trend towards mortality reduction for patients on low and high flow oxygen, and a trend towards increased mortality for those on mechanical ventilation. There was inconclusive effect on those without oxygen support. Remdesivir showed benefit in decreasing clinical deterioration, improving recovery rate, and reducing the need for mechanical ventilation. There was inconclusive effect on the need for ICU admission. The overall certainty of evidence was low due to serious risk of bias and inconsistency or imprecision in several critical outcomes.

Based on this review, remdesivir shows benefit in the treatment for patients with mild, moderate, and severe COVID-19 infection. However, there was no benefit in mortality noted among those with critical disease requiring mechanical ventilation. Remdesivir demonstrated a good safety profile, with no increased risk of adverse events compared to control. These results are consistent with the international agencies' recommendations for the use of remdesivir among patients with mild, moderate, or severe COVID-19 infection, but not for those with critical infection. These results are also similar with the 2022 systematic review on the use of remdesivir for COVID-19.[19]

Remdesivir is available in the Philippines as 100mg of lyophilized powder for reconstitution in a single-use vial, under a compassionate special permit (CSP) for use in the treatment of COVID-19.[20] The suggested retail price specified in a DOH memorandum is up to Php 8,200 per 100mg vial.[21] Using the dosing of 200mg IV on Day 1 and 100mg IV on Days 2 to 10 for a 10-day course, the total cost per patient (at the SRP) is Php 90,200.00. Remdesivir has been granted emergency use authorization by the US FDA for the treatment of COVID-19 in adults and children aged ≥28 days and weighing ≥3 kg.

Based on the available evidence, the consensus panel voted for the use of remdesivir among hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor for progression to severe disease. (Low quality of evidence; weak recommendation). They also voted for the use of remdesivir (3 days) among non-hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor for progression to severe disease. (Moderate quality of evidence; strong recommendation). They also voted for the use of remdesivir in children (hospitalized or ambulatory) with mild to moderate COVID-19 infection with at least 1 risk factor for disease progression. (Very low quality of evidence, weak recommendation) Risk factors for progression include age 60 years old or older, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease.

The consensus panel voted for the addition of remdesivir to dexamethasone in adult patients with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation. (Low quality of evidence; weak recommendation) For patients who progress to invasive mechanical ventilation while on remdesivir, the drug can be continued. They also voted for the addition of remdesivir to dexamethasone in children with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation. (Very low quality of evidence, weak recommendation)

The consensus panel voted against the use of remdesivir among adult patients with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation. (Low certainty of evidence; weak recommendation), and against the use of remdesivir among children with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation. (Very low certainty of evidence; weak recommendation),

The recommendations made by the consensus panel were primarily due to the perceived net benefit of the drug, with consideration of other factors including safety, cost, and availability.

The limitation of this review process is that search of included studies was limited only to electronic databases that were freely available. Electronic databases requiring paid subscription were not accessible to the authors; hence, studies published in these databases could not be reviewed.

CONCLUSION

Current evidence supports the use of remdesivir as treatment for patients with mild to moderate COVID-19, as well as in adult patients with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation.

Acknowledgments

This review is an update of the previous review on remdesivir done by Carol Stephanie C. Tan Lim, MD, MSc, April P. Padua-Zamora, MD, Mary Christine Castro, MD, MSc (adult population), and Melissa A. Dator, MD, Ma. Lucila M. Perez, MD, MSc, FPPS, Maria Teresa S. Tolosa, MD, FPDS, DipCE; Leonila F. Dans, MD, MS (pediatric population).

Registration

This review is registered with the University of the Philippines Manila Research Grants Administration Office (RGAO-2023-0147). Review protocol is available upon request with corresponding author. No amendments were made to the protocol during study implementation.

Data Availability

Data collection forms and data sets used for analysis are available upon request with corresponding author.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors received honorarium from the Department of Health for completing this review as part of the project entitled Philippine COVID-19 Living Clinical Practice Guidelines. The funding agency had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Funding Source

The study was funded by the Department of Health.

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APPENDICES

Appendix 1. Search Strategy and Results

Database	Search strategy / Search terms	Date and time of search	Results	
			Yield	Eligible
Medline https://pubmed.ncbi.nlm.nih.gov/	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir) Filters: January 01, 2022 to September 4, 2022	4 September 2022, 1500	387	1
CENTRAL https://www.cochranelibrary.com/dvanced-search	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir) Filters: January 2022 to September 4, 2022	4 September 2022, 1500	87	1
COVID-NMA initiative https://covid-nma.com/	(remdesivir)	4 September 2022, 1500	14	0

Appendix 1. Search Strategy and Results *(continued)*

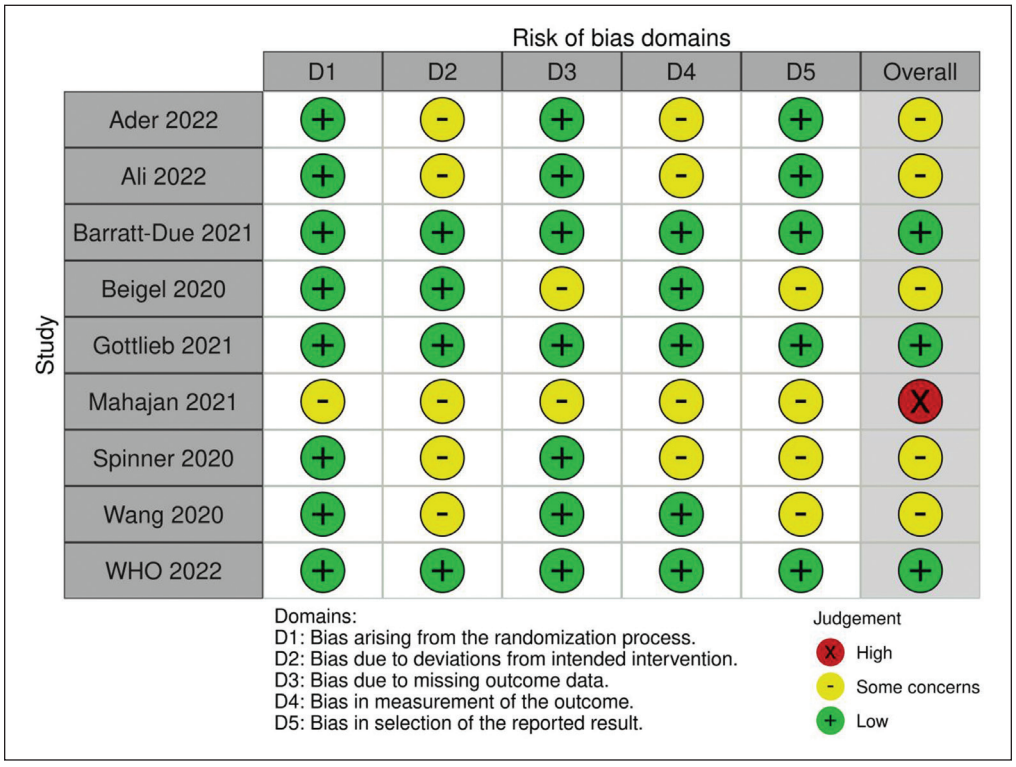
Database	Search strategy / Search terms	Date and time of search	Results	
			Yield	Eligible
Ongoing trials				
ClinicalTrials.gov https://clinicaltrials.gov/	covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	4 September 2022, 1500	118	32
Chinese Clinical Trial Registry http://www.chictr.org.cn/searchprojen.aspx	remdesivir	4 September 2022, 1500	0	0
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	covid 19 AND remdesivir	4 September 2022, 1500	3	1
Republic of Korea – Clinical Research Information Service https://cris.nih.go.kr/cris/info/introduce.do?search_lang=E&lang=E	remdesivir	4 September 2022, 1500	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search https://rctportal.niph.go.jp/en/	remdesivir	4 September 2022, 1500	8	0
CenterWatch https://www.centerwatch.com/clinical-trials/listings/	remdesivir	4 September 2022, 1500	20	2
Preprints				
chinaxiv.org	remdesivir	4 September 2022, 1500	0	0
Medrxiv.org	Remdesivir Filters: January to September 4, 2022	4 September 2022, 1500	201	0
Biorxiv.org	Remdesivir Filters: January to September 4, 2022	4 September 2022, 1500	83	0

Appendix 2. Characteristics of Included Studies

Title/Author	Country	Number of patients	Population	Intervention group(s)	Control	Outcome/s
Wang, 2020[6]	China	237 randomized, 226 evaluated	Severe COVID-19 patients Follow-up time: up to Day 28	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2–D10	Placebo	Clinical status (6-point ordinal scale) Clinical improvement (2 points reduction from baseline, or discharge from hospital) Time to clinical improvement Viral load Mortality Adverse events
WHO Solidarity Consortium, 2022[7]	Europe Canada Latin America Asia Africa	14,221 total randomized, 8,275 allocated 1:1 to remdesivir and control	Patients hospitalized with COVID-19 Follow-up time: up to Day 60	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2–D10 Other arms: Lopiravir/Ritonavir Hydroxychloroquine Interferon beta 1a	Standard of care	Mortality Use of mechanical ventilation Duration of hospitalization
Beigel, 2020[8]	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	1062 randomized, 1048 evaluated	Severe COVID-19 patients Follow-up time: up to Day 29	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2–D10	Placebo	Clinical status (using 8-category ordinal scale) Time to recovery (1-2 category change from baseline) Mortality Adverse events
Ader, 2022 (Final results)[9]	Austria Belgium France Luxembourg Portugal	857 randomized, 843 evaluated	Hospitalized COVID-19 patients requiring oxygen and/or ventilatory support Follow-up time: up to Day 90	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2–D10	Standard of care	Clinical status on day 15 Viral load Mortality Adverse events

Appendix 2. Characteristics of Included Studies *(continued)*

Title/Author	Country	Number of patients	Population	Intervention group(s)	Control	Outcome/s
Mahajan, 2021[10]	India	82 randomized, 70 evaluated	Moderate to severe COVID-19 Follow-up time: up to Day 24	Remdesivir 200 mg IV on D1, followed by 100 mg on D2-D5	Standard of care	Clinical status on day 12 (6-point ordinal scale) Mortality Safety outcomes (liver and renal function tests)
Spinner, 2020[11]	USA Europe UK Asia	596 randomized, 584 evaluated	Hospitalized patients with moderate COVID-19 Follow-up time: up to Day 28	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2–D10 Remdesivir 200 mg IV on D1, followed by 100 mg on D2-D5	Standard of care	Clinical status on day 11 (7-point ordinal scale) Clinical improvement (2-category change from baseline) Time to recovery Adverse events
Barratt-Due, 2021[12]	Norway	101 randomized, 83 completed, 3 month follow up	Hospitalized adults with COVID-19 Follow-up time: up to Day 90	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2–D10	Standard of care	Mortality Need for mechanical ventilation ICU admission Viral load Adverse events
Gottlieb, 2021[13]	United States Spain Denmark United Kingdom	584 randomized, 562 evaluated	Non-hospitalized patients with mild to moderate COVID-19 with risk factors for progression to severe disease within 7 days of symptom onset Follow-up time: Up to Day 28	Remdesivir 200 mg IV on D1, followed by 100 mg IV on D2–D3	Placebo	COVID-19 related hospitalization or death from any cause by Day 28 COVID-19 related medically attended visit or death from any cause by Day 28 Adverse events
Ali, 2022[14]	Canada	1,282 randomized, 1,281 analyzed	Hospitalized patients with laboratory confirmed SARS-CoV-2 infection Follow up: 28 days	Remdesivir 200 mg IV on D0, followed by 100 mg IV on Day 1-9	Standard of care	Mortality, need for mechanical ventilation, hospital length of stay, clinical severity of illness (WHO ordinal scale), adverse events (hepatic dysfunction and need for renal replacement therapy)



Appendix 3. Critical Appraisal of Included Studies

Appendix 4. GRADE Evidence Profile

Author(s): Carol Stephanie C. Tan Lim, MD, MSc
Question: Remdesivir compared to Placebo/Standard Care for COVID-19 hospitalized adult patients

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consi-derations	Remdesivir	Placebo / Standard Care	Relative (95% CI)	Absolute (95% CI)		
Mortality (Day 28)												
8	randomised trials	serious[a]	not serious	not serious	serious[b]	none	846/6352 (13.3%)	924/6087 (15.2%)	RR 0.90 (0.83 to 0.98)	15 fewer per 1,000 (from 26 fewer to 3 fewer)	⨁⨁◯◯ LOW	CRITICAL
Clinical improvement												
4	randomised trials	serious[c]	not serious	not serious	serious[b]	none	715/1024 (69.8%)	455/748 (60.8%)	RR 1.07 (1.01 to 1.13)	43 more per 1,000 (from 6 more to 79 more)	⨁⨁◯◯ LOW	CRITICAL
Clinical deterioration												
5	randomised trials	serious[c]	not serious	not serious	not serious	none	189/1565 (12.1%)	229/1269 (18.0%)	RR 0.75 (0.61 to 0.89)	45 fewer per 1,000 (from 69 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation												
4	randomised trials	serious[d]	serious[e]	not serious	not serious	none	693/5162 (13.4%)	851/5137 (16.6%)	RR 0.68 (0.51 to 0.90)	53 fewer per 1,000 (from 81 fewer to 17 fewer)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events												
5	randomised trials	serious[f]	not serious	not serious	serious[g]	none	341/2139 (15.9%)	354/1870 (18.9%)	RR 0.84 (0.65 to 1.09)	30 fewer per 1,000 (from 66 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												
5	randomised trials	serious[f]	not serious	not serious	not serious	none	941/2158 (43.6%)	790/1875 (42.1%)	RR 0.99 (0.92 to 1.08)	4 fewer per 1,000 (from 34 fewer to 34 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

Explanations:
[a] *Issues with randomization, performance bias, detection bias, missing outcome data, and reporting bias in majority of studies*
[b] *Upper or lower limit of confidence interval near no-effect value*
[c] *1 study with high risk of bias, the rest with overall some concerns for bias*
[d] *3 studies with overall some concerns for bias due to issues with deviation from intended intervention (2 studies), missing outcome data (1 study), outcome measurement bias (2 studies) and reporting bias (1 study)*
[e] *Significant heterogeneity*
[f] *All studies with some concern for bias due to issues with deviation from intended intervention, missing outcome data, outcome measurement bias and reporting bias*
[g] *Wide confidence interval*

Appendix 4. GRADE Evidence Profile *(continued)*

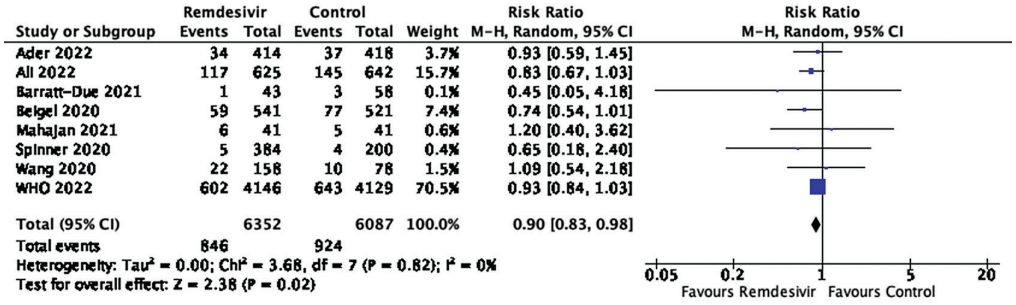
Author(s): Mary Christine Castro, MD,MSc, Carol Stephanie C. Tan Lim, MD, MSc
Question: Remdesivir compared to Placebo/Standard Care for non-hospitalized adult patients with COVID-19

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo / Standard Care	Relative (95% CI)	Absolute (95% CI)		
COVID-related hospitalization												
1	randomised trial	not serious	not serious	not serious	Serious[a]	none	2/279 (0.7%)	15/283 (5.3%)	RR 0.13 (0.03 to 0.59)	46 fewer per 1,000 (from 51 fewer to 32 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
COVID-related medically attended visits by Day 28												
1	randomised trial	not serious	not serious	not serious	Serious[a]	none	4/246 (1.6%)	21/252 (8.3%)	RR 0.19 (0.07 to 0.56)	68 fewer per 1,000 (from 77 fewer to 37 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
All-cause hospitalization by Day 28												
1	randomised trials	not serious	not serious	not serious	Serious[a]	none	5/279 (1.8%)	18/283 (6.4%)	RR 0.28 (0.10 to 0.75)	46 fewer per 1,000 (from 57 fewer to 16 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Alleviation of symptoms by Day 14												
1	randomised trials	not serious	not serious	not serious	Serious[b]	none	23/66 (34.8%)	15/60 (25.0%)	RR 1.41 (0.73 to 2.69)	102 more per 1,000 (from 68 fewer to 423 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events												
1	randomised trials	not serious	not serious	not serious	Serious[b]	none	118/279 (42.3%)	131/283 (46.3%)	RR 0.90 (0.75 to 1.09)	46 fewer per 1,000 (from 116 fewer to 42 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	Serious[a]	none	5/279 (1.8%)	19/283 (6.7%)	RR 0.26 (0.10 to 0.70)	50 fewer per 1,000 (from 60 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

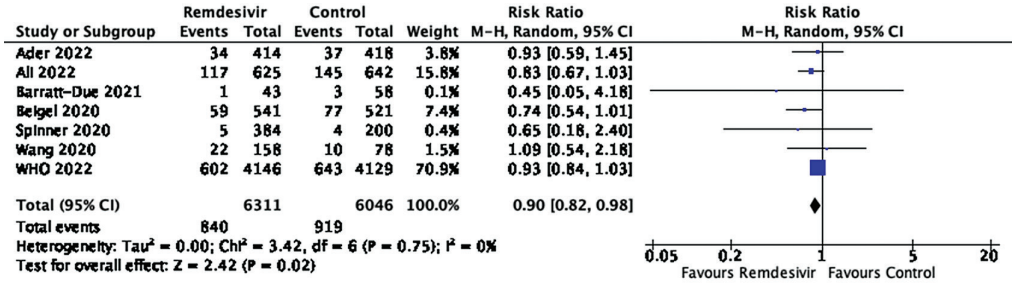
CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio

Explanations:
[a] Study did not reach target sample size due to administrative reasons, small number of events not reaching optimal information size
[b] Wide confidence interval

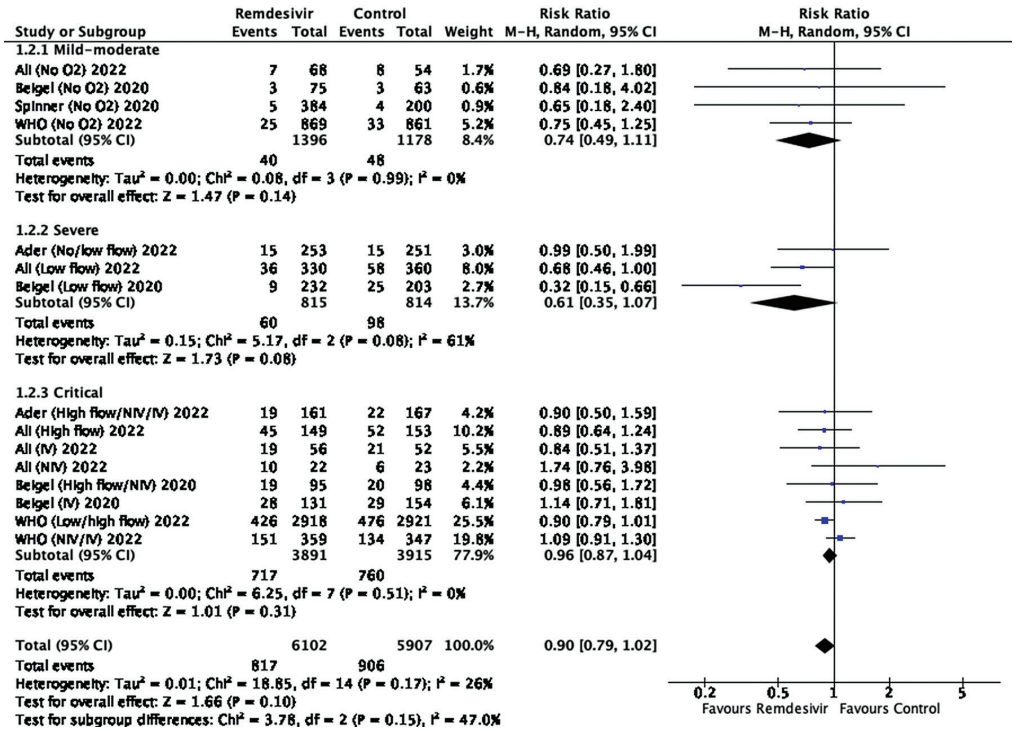
Appendix 5. Forest plots



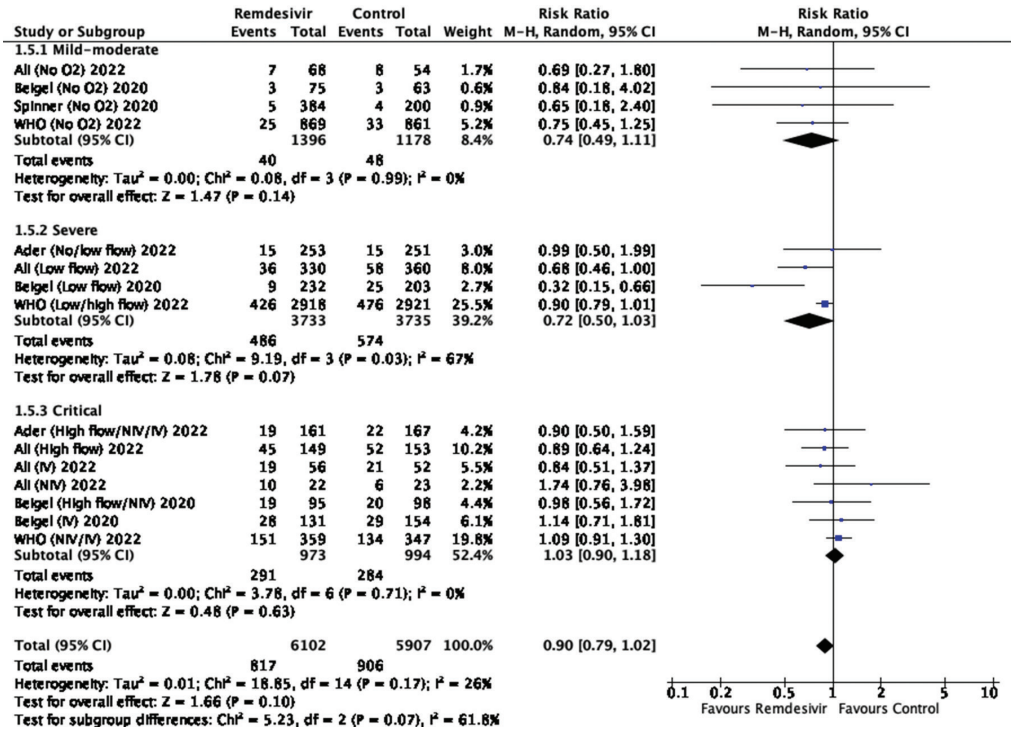
Appendix Figure 5A. Pooled effect of remdesivir on all-cause mortality at Day 28 among hospitalized patients.



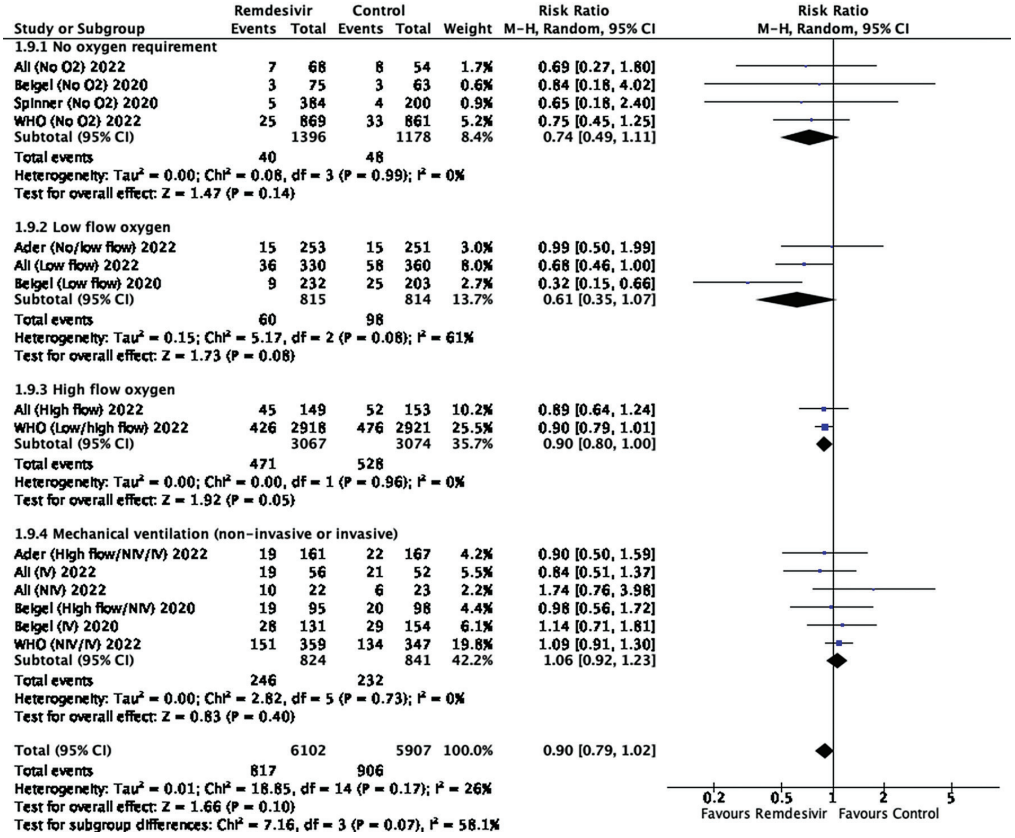
Appendix Figure 5B. Pooled effect of remdesivir on all-cause mortality at Day 28 among hospitalized patients (sensitivity analysis excluding studies with very serious risk of bias).



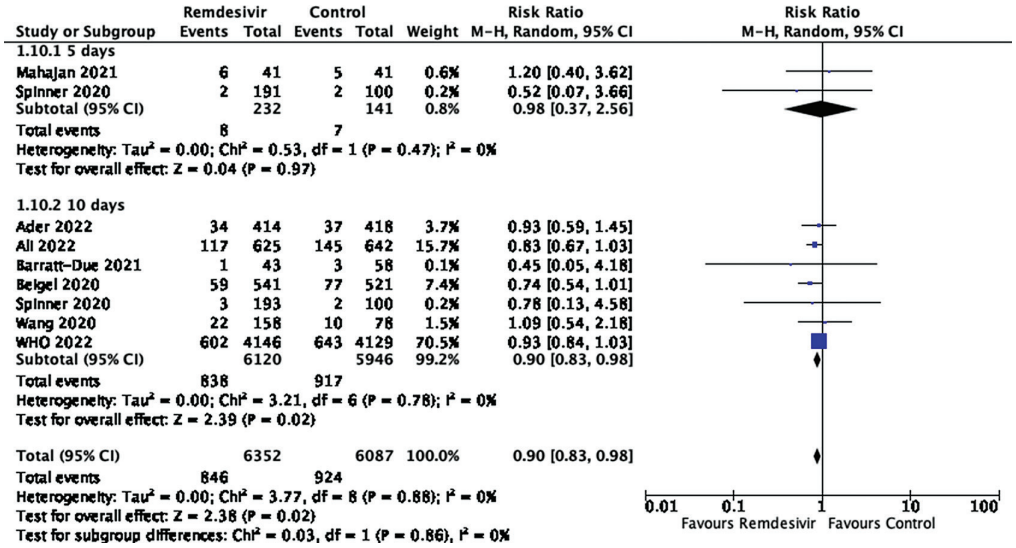
Appendix Figure 5C. Subgroup analysis for mortality by disease severity.



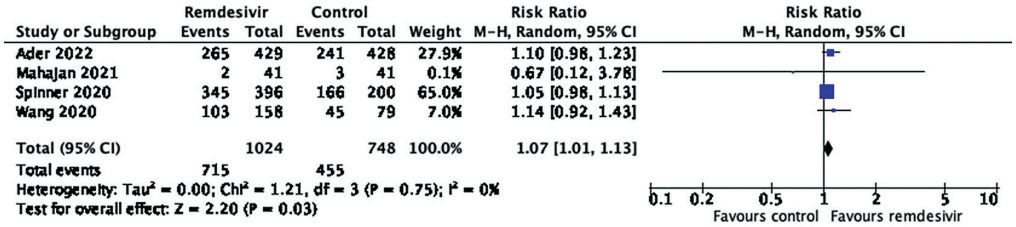
Appendix Figure 5D. Sensitivity analysis for the subgroup analysis for mortality by disease severity (WHO low/high flow oxygen placed in the severe subgroup).



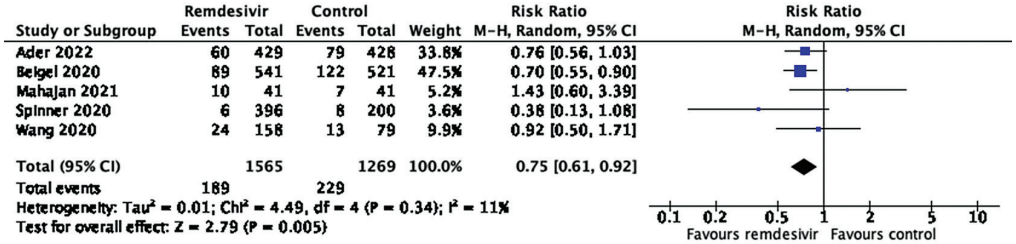
Appendix Figure 5E. Subgroup analysis for mortality by oxygen requirement.



Appendix Figure 5F. Subgroup analysis for mortality by treatment duration.



Appendix Figure 5G. Pooled effect of remdesivir on clinical improvement up to Day 28 among hospitalized patients.



Appendix Figure 5H. Pooled effect of remdesivir on clinical deterioration using the WHO progression score among hospitalized patients.

Appendix 6. Characteristics of Ongoing Studies

No.	Study Title	Interventions	Status
1	Factorial Randomized Trial of Remdesivir and Baricitinib Plus Dexamethasone for COVID-19 (the AMMURAVID Trial)	Drug: Baricitinib Oral Tablet [Olumiant] Drug: Remdesivir Drug: Dexamethasone	Not yet recruiting
2	IFN-beta 1b and Remdesivir for COVID19	Drug: Interferon beta-1b Drug: Remdesivir	Recruiting
3	Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to <18 Years of Age With Coronavirus Disease 2019 (COVID-19)	Drug: Remdesivir	Recruiting
4	Remdesivir in COVID-19 Lahore General Hospital	Drug: Remdesivir	Recruiting
5	Remdesivir, Long-covid and Quality of Life	Drug: Remdesivir	Recruiting
6	Baricitinib in Hospitalized Covid-19 Patients With Diabetes Mellitus	Drug: Baricitinib Drug: Dexamethasone Drug: Remdesivir	Recruiting
7	Efficacy of Remdesivir and Baricitinib for the Treatment of Severe COVID-19 Patients	Drug: Remdesivir Drug: Baricitinib Drug: Tocilizumab	Recruiting
8	Efficacy of Favipiravir in Treatment of Mild & Moderate COVID-19 Infection in Nepal	Drug: Favipiravir Drug: Placebo Drug: Remdesivir	Recruiting
9	ACTIV-5 / Big Effect Trial (BET-C) for the Treatment of COVID-19	Drug: Danicopan Other: Placebo Drug: Remdesivir	Recruiting
10	Comparative Therapeutic Efficacy and Safety of Different Antiviral and Anti Inflammatory Drugs in COVID-19 Patients.	Drug: Remdesivir Drug: Hydroxychloroquine Drug: Tocilizumab Drug: Lopinavir/ Ritonavir Drug: Ivermectin	Recruiting
11	Safety, Tolerability and Pharmacokinetics of Inhaled Nanoparticle Formulation of Remdesivir (GS-5734) and NA-831	Drug: NA-831 Drug: Placebo Drug: GS-5734 Combination Product: Drugs: NA-831 plus GS-5734	Recruiting
12	Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	Drug: Baricitinib Drug: Remdesivir + baricitinib Drug: Remdesivir Drug: Tocilizumab	Recruiting
13	Trial of Treatments for COVID-19 in Hospitalized Adults	Drug: Remdesivir Drug: Lopinavir/ritonavir Drug: Interferon Beta-1A Drug: Hydroxychloroquine Other: Standard of care Drug: AZD7442 Other: Placebo	Recruiting
14	ACTIV-3b: Therapeutics for Severely Ill Inpatients With COVID-19	Biological: Remdesivir Drug: Remdesivir Placebo Biological: Aviptadil Drug: Aviptadil Placebo Drug: Corticosteroid	Recruiting
15	Austrian CoronaVirus Adaptive Clinical Trial (COVID-19)	Drug: Chloroquine or Hydroxychloroquine Drug: Lopinavir/Ritonavir Other: Best standard of care Drug: Rivaroxaban Drug: Thromboprophylaxis Drug: Candesartan Drug: non-RAS blocking antihypertensives Drug: Remdesivir Drug: Asunercept 400mg Drug: Asunercept 100mg Drug: Asunercept 25mg Drug: Pentaglobin	Recruiting

Appendix 6. Characteristics of Ongoing Studies *(continued)*

No.	Study Title	Interventions	Status
16	Trial to Determine the Efficacy/Safety of Plitidepsin vs Control in Patients With Moderate COVID-19 Infection	Drug: Plitidepsin Drug: Dexamethasone Drug: Remdesivir	Recruiting
17	I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients	Drug: Remdesivir Drug: Pulmozyme Drug: IC14 Drug: Celecoxib Famotidine Drug: Narsoplimab Drug: Aviptadil Acetate Drug: Cyclosporine	Recruiting
18	Finding Treatments for COVID-19: A Trial of Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV)	Drug: Favipiravir Drug: Monoclonal antibodies Drug: Ivermectin Other: No treatment Drug: Remdesivir	Recruiting
19	Assessment of utility of Remdesivir in Patients with Acute Kidney Injury or Chronic Kidney Disease in admitted COVID-19 patients	Drug: Remdesivir	Recruiting
20	REMdesivir-HU Clinical Study and Severe Covid-19 Patients	Drug: Remdesivir-HU	Not recruiting
21	Study to Evaluate the Efficacy and Safety of Remdesivir in Participants With Severely Reduced Kidney Function Who Are Hospitalized for Coronavirus Disease 2019 (COVID-19)	Drug: Remdesivir	Not recruiting
22	ACTIV-5 / Big Effect Trial (BET-B) for the Treatment of COVID-19	Biological: Lenzilumab Drug: Remdesivir	Not recruiting
23	SARS-CoV-2 Human Challenge Characterisation Study	Drug: Remdesivir	Not recruiting
24	ACTIV-3: Therapeutics for Inpatients With COVID-19	Biological: LY3819253 Drug: Placebo Biological: Remdesivir Biological: VIR-7831 Biological: BRII-196/BRII-198 Biological: AZD7442 Drug: MP0420	Not recruiting
25	Antiviral Activity and Safety of Remdesivir in Bangladeshi Patients With Severe Coronavirus Disease (COVID-19)	Drug: Remdesivir	Completed
26	Efficacy and Safety of Remdesivir and Tociluzumab for the Management of Severe COVID-19: A Randomized Controlled Trial	Drug: Remdesivir Drug: Tocilizumab	Completed
27	Study in Participants With Early Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation	Drug: Remdesivir	Completed
28	Remdesivir Efficacy In Management Of COVID-19 Patients	Drug: Remdesivir	Completed
29	Effectiveness of Remedesvir in COVID-19 Patients Presenting at Mayo Hospital Lahore	Drug: Remdesivir	Completed
30	ACTIV-5 / Big Effect Trial (BET-A) for the Treatment of COVID-19	Other: Placebo Drug: Remdesivir Biological: Risankizumab	Completed
31	Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	Drug: Baricitinib Drug: Dexamethasone Other: Placebo Drug: Remdesivir	Completed
32	The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients	Drug: Hydroxychloroquine Drug: Remdesivir Other: (Standard of Care) SoC	Unknown
33	Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to <18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN)	Drug: Remdesivir	Recruiting