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Review Article

Real-World Effectiveness of Remdesivir in Patients with Coronavirus Disease 2019 (COVID-19): A Systematic Review

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ABSTRACT

Background: COVID-19, caused by the SARS-CoV-2 virus, has been a global health crisis, affecting individuals of all ages and leading to complications like ARDS, sepsis, and multi-organ failure. The pandemic has notably impacted healthcare systems in countries like India and Indonesia. Remdesivir has emerged as a popular treatment option, but its real-world effectiveness remains a subject of debate due to varying patient demographics, disease severities, and healthcare settings.
Aim: This review aims to systematically analyse observational study data to evaluate the real-world efficacy of Remdesivir in treating COVID-19 patients across various global healthcare settings. It focuses on patients with moderate to severe COVID-19, synthesizing data to understand the role and benefits as well as potential limitations of Remdesivir in clinical practice.
Methods: The review protocol was registered with PROSPERO and involved comprehensive literature searches in databases like PubMed, the Cochrane Library, and Google Scholar. The search, spanning from the beginning of the pandemic until April 2022, focused on studies involving adult patients with severe or serious COVID-19 treated with Remdesivir. Data extraction followed a standardized form, and the quality of non-randomized studies was assessed using the ROBINS-I method. The review included a narrative synthesis due to the heterogeneity of the studies.
Results: The review analysed data from nine studies, revealing varied outcomes in terms of The World Health Organization (WHO) ordinal scale clinical improvement, mortality rates, need for oxygen support and hospital stay length. The results indicated that Remdesivir, particularly in combination with other treatments like corticosteroids, could have a positive impact on reducing symptom severity, mortality rates, and hospitalization duration in COVID-19 patients.
Conclusion: Remdesivir, as part of COVID-19 treatment Regimens, shows promise in real-world clinical settings, particularly in reducing the severity and mortality of the disease. However, Remdesivir effectiveness varies based on patient demographics, disease severity, and the healthcare environment. Future research should focus on long-term outcomes and the identification of patient subgroups that could benefit the most from Remdesivir.

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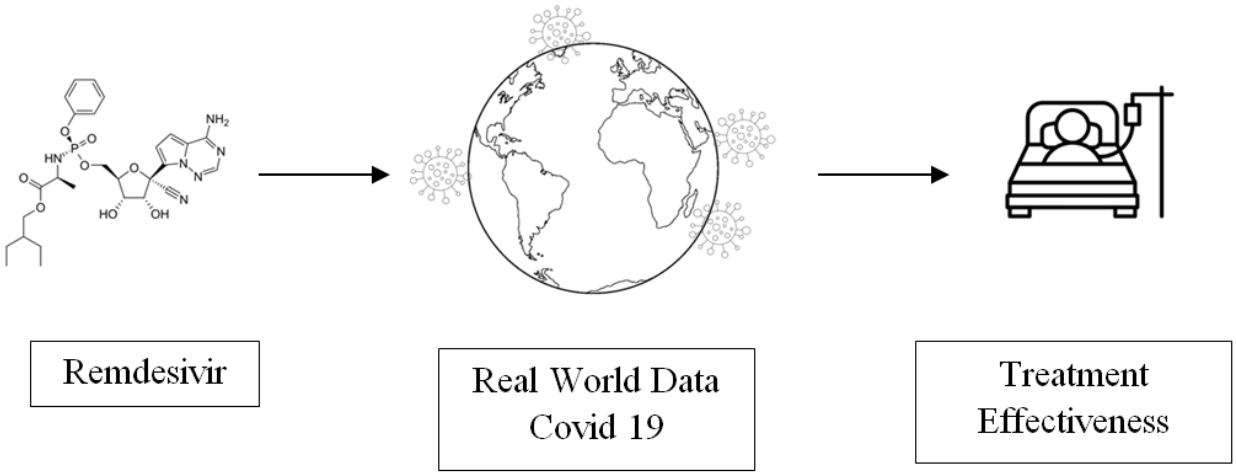
GRAPHICAL ABSTRACT



Introduction

The COVID-19 pandemic, triggered by the novel coronavirus SARS-CoV-2, has become a global health emergency affecting individuals of all ages. While the disease's severity varies, it can lead to critical complications such as acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure in certain populations [1]. The pandemic's impact has been diverse across different regions, with countries like India and Indonesia facing significant healthcare challenges. Indonesia, in particular, experienced considerable difficulty during its pandemic waves, becoming the epicentre in Asia for COVID-19, especially during the surge of the Delta variant [2, 3].

In response to this global crisis, a concentrated effort in medical research has been directed towards understanding SARS-CoV-2, developing effective vaccines, and identifying viable therapeutic agents [4]. Remdesivir has attracted significant attention among the therapeutic options. Various studies have evaluated its effectiveness, showing potential benefits in reducing the time to clinical improvement in hospitalized COVID-19 patients [1]. However, the efficacy and safety of Remdesivir continue to be explored through systematic reviews and meta-analyses, revealing differing conclusions regarding its impact on patient outcomes [1]. Recent studies have also explored the use of Remdesivir in combination therapies. Researchers examined the effects of using both corticosteroids and Remdesivir together versus corticosteroids alone in ventilated COVID-19 patients and found that the combination therapy might be more effective [1]. Moreover, real-world treatment patterns and clinical outcomes for hospitalized COVID-19 patients have been examined, offering insights into the practical application and effectiveness of Remdesivir alongside other treatments [4].

Despite the promising outcomes in some trials, the real-world effectiveness of Remdesivir remains a subject of debate. This is partly due to the variability in patient demographics, disease severity, and healthcare settings in the studies conducted. Observational studies, as opposed to randomized controlled trials (RCTs), offer insights into the drug's performance in more varied and less controlled environments, reflecting a broader spectrum of the global population and healthcare systems. This systematic and narrative review aims to collate and analyse data from these observational studies. It seeks to provide a comprehensive overview of Remdesivir's effectiveness in real-world scenarios, encompassing various stages of COVID-19, from mild to severe cases, and across

diverse global healthcare settings. By synthesizing data from a wide range of sources, this review endeavours to offer valuable insights into the role of Remdesivir in the on-going battle against COVID-19, highlighting its potential benefits and limitations in real-world clinical applications.

Materials and Methods

Protocol and registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42022316755.

Search strategy

An extensive and methodical literature search was conducted utilizing three key databases: PubMed, the Cochrane Library, and Google Scholar. This study aimed to identify scholarly articles pertinent to the administration of Remdesivir for COVID-19 treatment. The designated period for this search extended from the onset of the global pandemic, starting December 1st, 2019, until April 1st, 2022. This period was selected to capture the full scope of the evolving research on COVID-19 therapeutics through various stages of the pandemic.

The search was structured around a precise set of keywords: "COVID-19," "Remdesivir," and study design descriptors "Cohort" or "Case-control study." A comprehensive search strategy, including all utilized search terms, has been meticulously documented. For those wishing to review this strategy in detail, it is available at the following link: https://www.crd.york.ac.uk/PROSPEROFILES/316755_STRATEGY_20220417.pdf.

A manual review of the reference lists from the identified articles and pertinent review papers was undertaken to augment the electronic search and ensure the inclusion of all relevant publications.

In addition, an exploratory search for grey literature was executed to incorporate the latest and potentially unpublished studies, which included sourcing data from conference proceedings, preprint repositories, and registries of clinical trials. This grey literature often harbours valuable insights into current research endeavours that have not yet been formally published.

To ensure a thorough retrieval of studies that were in line with the review's objectives, a seasoned information specialist oversaw the development and execution of the search strategy with input from the research team. The entire search process was recorded thoroughly to uphold the principles of reproducibility and transparency, in line with the PRISMA guidelines.

Eligibility criteria

Inclusion criteria were adult patients diagnosed with severe or critical COVID-19, as confirmed by PCR or antigen swab testing. The study designs considered were cohort, case-control, and observational studies. Exclusion criteria included studies on adolescents (under 18 years of age), RCTs, and animal studies.

Intervention and comparator

The intervention under review was a fixed dose of Remdesivir administered for any duration. Comparators included COVID-19 patients who received antiviral therapy other than Remdesivir or standard treatment protocols for similar disease severities.

Outcomes

Primary outcomes included clinical improvement assessed by the WHO ordinal scale and mortality rates at day 7, day 14, and day 28. Secondary outcomes involved the length of hospital stay and the level of oxygen support required by patients. For these outcomes, measures such as mean difference (MD) with 95% confidence intervals (CI) and standard mean difference (SMD) with 95% CI were used. Categorical outcomes were evaluated using relative risk (RR) or hazard ratios (HR) with 95% CI. Additional outcomes of interest included cycle threshold values and PCR results.

Data extraction and quality assessment

Data were extracted from selected studies using a standardized form that captured author's name, year of publication, study setting, sample size, research design, intervention arm, control arm, and outcomes. The quality of non-randomized studies was appraised using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool (25), with critical appraisal conducted by two independent reviewers.

Data synthesis strategy

Data synthesis will be conducted narratively due to the heterogeneity of the included studies which precludes a quantitative meta-analysis. The narrative synthesis will summarise and explain the included studies' findings, considering factors such as study design, population, intervention, and outcomes. This approach will provide a descriptive analysis of the patterns and findings across the body of literature. The synthesis will aim to identify common themes, differences, and any factors that influence the effectiveness and safety of Remdesivir treatment in the management of COVID-19. The results will be structured around key outcomes and variables of interest to provide a comprehensive overview of the existing evidence.

Results and Discussion

The PRISMA flowchart from the attached document illustrates the meticulous process undertaken for selecting studies in the systematic review. Initially, the search across databases and websites yielded 863 records. After the removal of duplicates and ineligible records through automated tools, 366 records were screened based on title and abstract. This screening led to the exclusion of 294 records, largely due to irrelevance or not meeting the pre-defined criteria. The remaining 72 articles were considered for full-text retrieval, although only 15 were further assessed for eligibility after excluding those that were not retrievable or pertinent. The reasons for exclusion at this stage were specific and included the presence of alternative treatments or differing disease severities. Ultimately, the selection process was rigorous and detail-oriented, resulting in 9 studies that were thoroughly reviewed and included in the final analysis of the review.

Our systematic review encompasses a broad spectrum of outcomes from nine diverse articles, delving into the intricacies of treatment efficacy and patient outcomes in COVID-19 management. The studies explored multiple aspects ranging from the WHO ordinal scale to acute renal failure, discharge rates, ICU admissions, mortality in various settings, mechanical ventilation, oxygen therapy, ECMO usage, and hospital stay duration. The studies by Ayodele *et al.,* Gupta *et al.*, and Jeck *et al.,* 2021 [4-6], provide critical insights into COVID-19 treatment efficacy using the WHO ordinal scale, illustrating the nuances of patient response to different therapeutic Regimens. The study conducted by Ayodele *et al.* in 2021 [4] carefully examined the WHO ordinal scale scores over time to analyse how patient outcomes varied with different therapies. Remarkably, on the 28th day, a substantial percentage of patients receiving the Dexamethasone+Remdesivir treatment (Regimen 1) were found to be in the mildest category (Score 0: 3,273 patients, representing 84.1% of the total). The same pattern was observed in patients receiving Azithromycin+Dexamethasone+Remdesivir (Regimen 3) and Azithromycin+Remdesivir (Regimen 4), with 81.1% and 89.3% achieving a Score 0, respectively. The study findings indicate that these therapy Regimens have the ability to reduce the severity of COVID-19 symptoms. However, their effectiveness varied in comparison to the control groups, indicating a range of efficacy depending on the specific treatment combinations.

[5] examined the effects of Remdesivir, both as a standalone treatment and in combination with Tocilizumab. Remarkably, Remdesivir demonstrated a significant enhancement in the median WHO ordinal scale score (from 5.0 to 2.0) on its own. However, intriguingly, the inclusion of Tocilizumab resulted in a decline in the score. This result not only demonstrates the efficacy of Remdesivir as a single treatment, but also highlights the intricate relationship between drug interactions in the field of COVID-19 treatment.

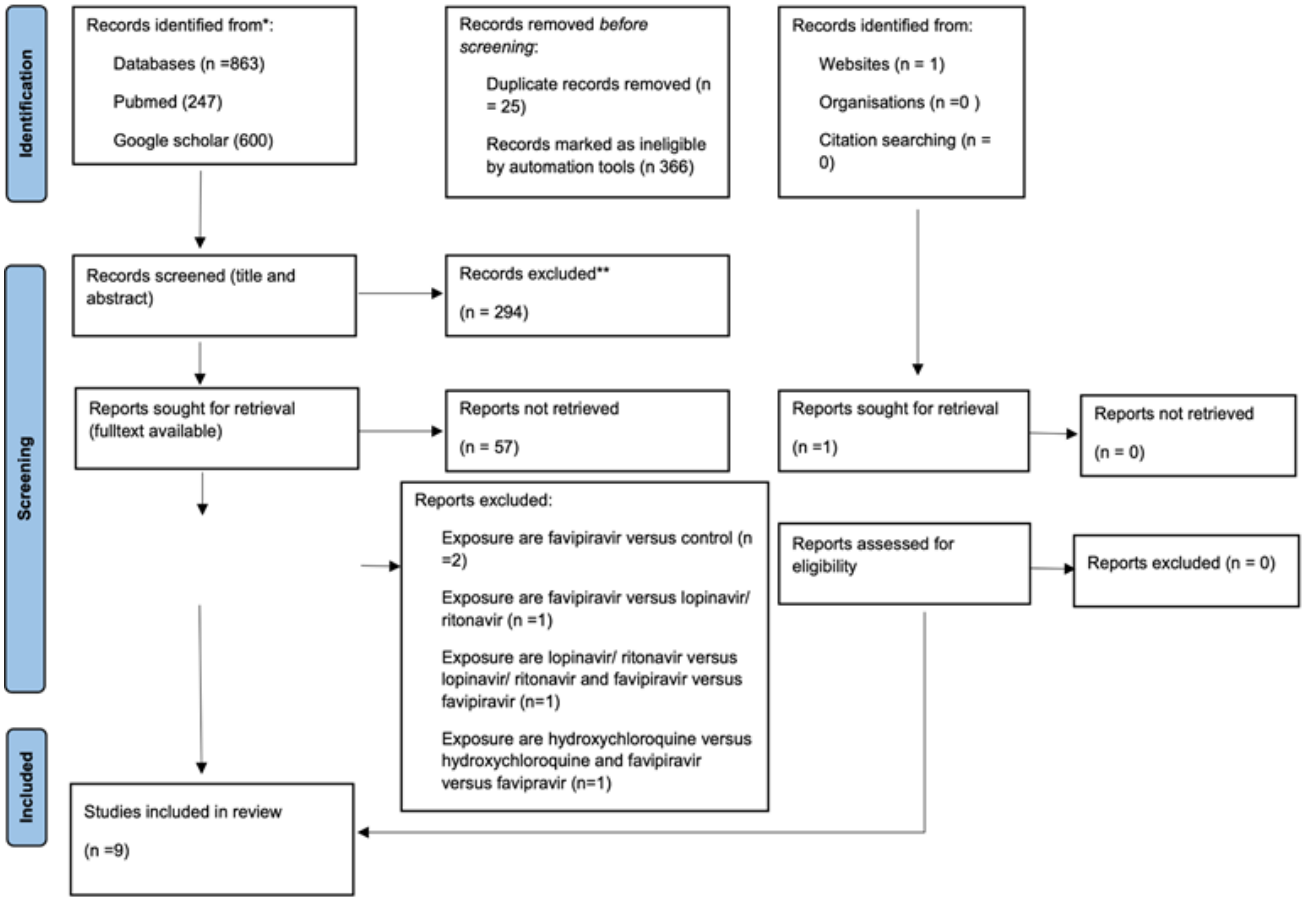


Figure 1: PRISMA flowchart

Table 1: Comparative analysis of COVID-19 treatment regimens

Author	Study design and Setting	Number of participants	Regimen	Effect on Intervention Arm	Effect on Control Arm	Realtive Risks and NNTs
Ayodele *et al.* [4]	Retrospective cohort study Adult COVID-19 patients in the US between September 2020 and January 2021 Databa	26192	-Intervention Arm: Regimen 1: Dexamethasone+Remdesivir Regimen 2: Remdesivir Regimen 3: Azithromycin+Dexamethasone+Remdesivir Regimen 4: Azithromycin+Remdesivir Regimen 5: Convalescent Plasma+Dexamethasone+Remdesivir -Control Arm:	Regimen 1 (Dexamethasone+Remdesivir): -WHO Ordinal Scale Day 28: Score 0: 3,273 (84.1%), Score 1: 70 (1.8%), Score 2: 52 (1.3%), Score 3: 496 (12.7%) -ICU: 360/3891 (9.3%)	Regimen 6 (Dexamethasone): -WHO Ordinal Scale Day 28: Score 0: 7,835 (84.5%), Score 1: 159 (1.796%), Score 2: 78 (0.8%), Score 3: 1,197 (12.9%)	Regimen 1 vs 6 (Dexamethasone+Remdesivir vs Dexamethasone): -WHO Ordinal Scale (Day 28): Score 0: RR: 0.995, 95% CI: 0.982 to 1.009, NNT: 200.0 Score 1: RR: 1.037, 95% CI: 1.016 to 1.058, NNT: 27.027 Score 2: RR: 1.138, 95% CI: 1.080 to 1.199, NNT: 7.246 Score 3: RR: 1.248, 95% CI: 1.117 to 1.396, NNT: 4.032

Author	Study design and Setting	Number of participants	Regimen	Effect on Intervention Arm	Effect on Control Arm	Realtive Risks and NNTs
	se used: The de-identified Optum 1 COVID-19 EHR database se		Regimen 6: Dexamethasone Regimen 7: Azithromycin+Dexamethahson Regimen 8: Azithromycin Regimen 9: Convalescent Plasma Regimen 10: Hydroxychloroquine Regimen 11: Azithromycin+Hydroxychloroquine	-Oxygen Supplementation: 253/3891 (6.5%) -ECMO: 1/3891 (<0.1%)	-ICU: 720/9269 (7.8%) -Oxygen Supplementation: 374/9269 (4.0%) -ECMO: 4/9269 (<0.1%)	-ICU: RR 1.191, 95% CI: 1.055 to 1.344, NNT: 67.372 -Oxygen Supplementation: RR 1.611, 95% CI: 1.380 to 1.882, NNT: 40.531 -ECMO: RR 0.595, 95% CI: 0.067 to 5.327, NNT: 5729.258
				Regimen 3 (Azithromycin+Dexamethasone+Remdesivir): -WHO Ordinal Scale Day 28: Score 0: 1,417 (81.1%), Score 1: 51 (2.9%), Score 2: 27 (1.5%), Score 3: 252 (14.4%) -ICU: 243/1747 (13.9%) -Oxygen Supplementation: 122/1747 (7.0%) -ECMO: 1/1747 (<0.1%)	Regimen 7 (Azithromycin+Dexamethasone): -WHO Ordinal Scale Day 28: Score 0: 2,758 (81.0%), Score 1: 87 (2.6%), Score 2: 36 (1.1%), Score 3: 524 (15.4%) -ICU: 352/3405 (10.3%) -Oxygen Supplementation: 182/3405 (5.3%) -ECMO: 0	Regimen 3 vs 7 (Azithromycin+Dexamethasone+Remdesivir vs Azithromycin+Dexamethasone): -WHO Ordinal Scale (Day 28): Score 0: RR: 1.001, 95% CI: 0.979 to 1.024, NNT: 1000.0 Score 1: RR: 1.091, 95% CI: 1.043 to 1.142, NNT: 10.989 Score 2: RR: 1.382, 95% CI: 1.272 to 1.501, NNT: 2.618 Score 3: RR: 1.482, 95% CI: 1.327 to 1.656, NNT: 2.075 -ICU: RR 1.345, 95% CI: 1.155 to 1.568, NNT: 27.997 -Oxygen Supplementation: RR 1.306, 95% CI: 1.046 to 1.631, NNT: 61.038 -ECMO: Specific RR

Author	Study design and Setting	Number of participants	Regimen	Effect on Intervention Arm	Effect on Control Arm	Realtive Risks and NNTs
						& NNT not applicable
				Regimen 4 (Azithromycin+Remdesivir): -WHO Ordinal Scale Day 28: Score 0: 549 (89.3%), Score 1: 17 (2.8%), Score 2: 6 (1.0%), Score 3: 43 (7.0%) -ICU: 46/615 (7.5%) -Oxygen Supplementation: 21/615 (3.4%) -ECMO: 0	Regimen 8 (Azithromycin): -WHO Ordinal Scale Day 28: Score 0: 2,945 (87.3%), Score 1: 65 (1.9%), Score 2: 16 (0.5%), Score 3: 347 (10.3%) -ICU: 163/3373 (4.8%) -Oxygen Supplementation: 100/3373 (3.0%) -ECMO: 0	Regimen 4 vs 8 (Azithromycin+Remdesivir vs Azithromycin): -WHO Ordinal Scale (Day 28): Score 0: RR: 1.022, 95% CI: 0.995 to 1.050, NNT: 45.455 Score 1: RR: 1.119, 95% CI: 1.082 to 1.157, NNT: 8.403 Score 2: RR: 1.200, 95% CI: 1.137 to 1.267, NNT: 5.0 Score 3: RR: 1.214, 95% CI: 1.070 to 1.375, NNT: 4.673 -ICU: RR 1.548, 95% CI: 1.129 to 2.122, NNT: 37.776 -Oxygen Supplementation: RR 1.152, 95% CI: 0.725 to 1.829, NNT: 222.265 -ECMO: Specific RR & NNT not applicable
Gupta *et al.* (5)	Retrospective cohort study at a public tertiary care hospital	521	Intervention Arm: Remdesivir Remdesivir +Tocilizumab Control Arm: Tocilizumab	-WHO Ordinal Scale: - Remdesivir: Median (IQR) 5.0(1.0) before, 2.0(7.0) after, change 3.0(6.0), days to change 11(9.5) - Remdesivir + Tocilizumab: Median (IQR) 5.0(1.0) before, 8.0(6.0) after, change -2.0(6.0), days to change 7.5(9.8)	-WHO Ordinal Scale: - Tocilizumab: Median (IQR) 5.0(1.0) before, 2.0(10) after, change 3.0(0.0), days to change 2.0(43(12.0))	-WHO Ordinal Scale: RR and NNT not provided

Author	Study design and Setting	Number of participants	Regimen	Effect on Intervention Arm	Effect on Control Arm	Realtive Risks and NNTs
				-Discharge: - Remdesivir: 273/414 (66.4%) - Remdesivir+Tocilizumab: 36/76 (47.4%) -In-hospital mortality: - Remdesivir: 141/414 (33.6%) - Remdesivir+Tocilizumab: 40/76 (52.6%) -Duration of Hospitalization (days): - Remdesivir: 14 - Remdesivir+Tocilizumab: 10	-Discharge: - Tocilizumab: 25/31 (80.6%) -In-hospital mortality: - Tocilizumab: 6/31 (19.4%) -Duration of Hospitalization (days): - Tocilizumab: 47	-Discharge: RR 0.587 (95% CI 0.438 to 0.787), NNT 3.005 -In-hospital mortality: RR 2.719 (95% CI 1.285 to 5.754), NNT 3.005 -Duration of Hospitalization: RR and NNT not provided
Jeck *et al.* (6)	Retrospective cohort study, Population of Cologne, Germany, Inhospital COVID-19 patients	1152	Intervention Arm: Remdesivir (5-6 of 8 ordinal scale) Control Arm: No Remdesivir	-WHO Ordinal Scale at Day 15: - Scores 1-3: 293/576 (50.8%) - Score 4: 48/576 (8.4%) - Score 5: 57/576 (9.9%) - Score 6: 25/576 (4.3%) - Score 7: 110/576 (19.1%) - Score 8: 43/576 (7.5%) -Number of Discharges: 293/576 (50.85%) -ICU Admission Needed: 178/576 (30.90%) -Length of Stay: 25.6	-WHO Ordinal Scale at Day 15: - Scores 1-3: 259/576 (45.0%) - Score 4: 37/576 (6.4%) - Score 5: 66/576 (11.4%) - Score 6: 26/576 (4.5%) - Score 7: 125/576 (21.7%) - Score 8: 63/576 (11.0%) -Number of Discharges: 259/576 (44.96%)	-WHO Ordinal Scale at Day 15: - RR 7.618 (95% CI 5.431-10.685), NNT 2.560 for scores 1-3 - RR 0.683 (95% CI 0.471-0.988), NNT 28.800 for score 8 -Number of Discharges: RR 1.131 (95% CI 1.002-1.277), NNT 16.941 -ICU Admission Needed: RR 0.832 (95% CI 0.707-0.978), NNT 16.000 -Length of Stay: RR and NNT not provided

Author	Study design and Setting	Number of participants	Regimen	Effect on Intervention Arm	Effect on Control Arm	Realtive Risks and NNTs
				days	-ICU Admission Needed: 214/576 (37.15%) -Length of Stay: 57.0 days	
Falcão *et al.* [7]	Prospective cohort study conducted at Centro Hospitalar de Lisboa Ocidental, Portugal.	149	Intervention Arm: Remdesivir, 200 mg on day 1 followed by 100 mg once daily for 5 or 10 days Control Arm: HCQ-based regimens (HCQ 400 mg on day 1, followed by 200 mg twice daily for 5–10 days)	-Acute Renal Failure: 1/48 (2.1%) -Hospital Stay (Days): Average 18.0 days (SD: ±11.33)	-Acute Renal Failure: 8/101 (7.9%) -Hospital Stay (Days): Average 22.0 days (SD: ±20.9)	-Acute Renal Failure: RR 0.263 (95% CI 0.034 to 2.044), NNT 17.131 -Hospital Stay: RR and NNT not provided
Elec *et al.* [8]	Retrospective cohort study, Clinical Institute of Urology and Renal Transplantation, Cluj-Napoca, Romania	165	Intervention Arm: HCQ 400 mg 2x/day at first day and 200 mg BDs for 7–10 days For mild and moderate cases: Lopinavir/Ritonavir, darunavir/ritonavir, or darunavir/cobicistat For severe cases: RDV 200 mg at first day, and 100 mg for 4 days Control Arm: Standard of care HCQ 400 mg BDs at first day and 200 mg BDs for 7–10 days	• Acute Renal Failure: 19/38 (50%) • ICU Admission: 18/38 (47%) • Overall Mortality: 7/38 (18%) • ICU Mortality: 7/38 (18%) • Mechanical Ventilation: 8/38 (21%) • Oxygen Therapy: 32/38 (84%)	• Acute Renal Failure: 55/127 (43%) • ICU Admission: 35/127 (27%) • Overall Mortality: 29/127 (23%) • ICU Mortality: 29/127 (23%) • Mechanical Ventilation: 30/127 (24%) • Oxygen Therapy: 56/127 (44%)	• Acute Renal Failure: RR 1.910 (95% CI 1.503-2.426), NNT 2.493 • ICU Admission: RR 1.732 (95% CI 1.118-2.685), NNT 4.994 • Overall Mortality: RR 0.806 (95% CI 0.384-1.693), NNT 22.657 • ICU Mortality: RR 0.851 (95% CI 0.471-1.781, NNT 29.497 • Mechanical Ventilation: RR 0.891 (95% CI 0.447-1.778), NNT 38.919 • Oxygen Therapy: RR 1.343 (95% CI 0.845-2.13), NNT 10.649

Author	Study design and Setting	Number of participants	Regimen	Effect on Intervention Arm	Effect on Control Arm	Realtive Risks and NNTs
Bechman *et al.* [9]	Retrospective cohort study, King's College Hospital, Camberwell and Princess Royal University Hospital, Bromley	3949	Intervention Arm: Remdesivir Control Arm: No Remdesivir	• Discharged: 1576/1917 (81.7%) • Admitted to ICU: 418/1917 (21.8%) • 28-day In-Hospital Mortality: 332/1917 (17.3%)	• Discharged: 1628/2032 (80.1%) • Admitted to ICU: 223/2032 (11.0%) • 28-day In-Hospital Mortality: 401/2032 (19.7%)	• Discharged: RR 1.026 (95% CI 0.996-1.057), NNT 47.763 • Admitted to ICU: RR 1.911 (95% CI 1.649-2.215), NNT 9.62 • 28-day In-Hospital Mortality: RR 0.878 (95% CI 0.77-1.00), NNT 41.399
Mandadi *et al.* [1]	Retrospective cohort study, Data from TriNetX (HIPAA)	148	Intervention Arm: RDV 200 mg at first day, and 100 mg on days 2–5 or until hospital discharge or death Dexamethasone 6 mg ODs or equivalent doses of methylprednisolone 32mg ODs, or hydrocortisone 160mg ODs Control Arm: Dexamethasone 6 mg ODs or equivalent doses of methylprednisolone 32mg ODs, or hydrocortisone 160mg ODs	• 28-Day All-Cause In-Hospital Mortality: 27/74 (36.5%) • Length of Stay (Days): 13.4	• 28-Day All-Cause In-Hospital Mortality: 22/74 (29.7%) • Length of Stay (Days): 13.4	• 28-Day Mortality: RR 1.227 (95% CI 0.773-1.947), NNT 14.80 • Length of Stay: RR and NNT not provided
Mozzaffari *et al.* [10]	Retrospective Cohort study, Premier healthc	57710	Intervention Arm: Remdesivir Control Arm: Non Remdesivir	• IMV/ECMO within 14 days: 419/1296 (32.3%) • IMV/ECMO within 28 days: 627/1296 (48.4%) • Overall	• IMV/ECMO within 14 days: 568/1296 (43.8%) • IMV/ECMO within 28	• IMV/ECMO within 14 days: HR 0.70 (95% CI 0.58-0.84) • IMV/ECMO within 28 days: HR 0.81 (95% CI 0.69-

Author	Study design and Setting	Number of participants	Regimen	Effect on Intervention Arm	Effect on Control Arm	Realtive Risks and NNTs
	are database			Mortality within 14 days: 3001/28855 (10.6%) • Overall Mortality within 28 days: 4444/28855 (15.4%)	days: 723/1296 (55.8%) • Overall Mortality within 14 days: 4328/28855 (15.4%) • Overall Mortality within 28 days: 5511/28855 (19.1%)	0.94) • Overall Mortality within 14 days: HR 0.76 (95% CI 0.69-0.83) • Overall Mortality within 28 days: HR 0.88 (95% CI 0.81-0.96)
Almaghlouth *et al.* [11]	Retrospective cohort study, Four medical centers in El Paso, Texas	113	Intervention Arm: Remdesivir Tocilizumab 4 mg/kg/day QDs Methylprednisolone 60 mg TDs Control Arm: Tocilizumab 4 mg/kg/day QDs Methylprednisolone 60 mg TDs	-In-hospital mortality: 6 out of 33 (18.18%) -Mechanical ventilation: 9 out of 33 (27.27%)	-In-hospital mortality: 7 out of 80 (8.75%) -Mechanical ventilation: 9 out of 80 (11.25%)	-In-hospital mortality: RR 2.052 (95% CI 0.746-5.645), NNT 10.134 -Mechanical ventilation: RR 2.424 (95% CI 1.057-5.561), NNT 6.241

A separate analysis [6], offered a novel viewpoint by analysing results only on Day 15. Their findings revealed that a significant proportion of patients in the Remdesivir group (50.8%) fell into the mild to severe severity category (Scores 1-3). This statistic, in conjunction with the relative risk analysis, further supports the beneficial effect of Remdesivir in reducing the progression to more severe stages of the disease.

Collectively, these studies provide a detailed depiction of the dynamic and diverse characteristics of therapy approaches for COVID-19. They clearly emphasize the effectiveness of particular medicines, such as Remdesivir, when used in different combinations, while also noting the varying effects of mixed therapy Regimens. The knowledge obtained from this study is extremely valuable, contributing to the overall understanding of clinical decision-making and advancing the effort to improve treatment protocols in the on-going fight against COVID-19.

An essential component of comprehending the management of COVID-19 is the investigation of mortality outcomes of its treatment. By examining in-hospital mortality, death within certain periods (14 and 28 days), and ICU mortality, six studies have made substantial contributions to our comprehension of this matter, each employing unique methodologies. These articles collectively provide a detailed and subtle viewpoint on how various treatment Regimens affect the survival of patients.

One study in 2021 [5] revealed that the concurrent administration of Remdesivir and Tocilizumab resulted in a significant rise in in-hospital mortality (52.6%), as compared to the use of Tocilizumab alone (19.4%). These findings indicate the possibility of problems or lack of efficacy when these medications are combined.

The study's relative risk (RR) analysis confirmed this observation, indicating a significant rise in the risk of mortality with the combo medication (RR 2.7193, 95% CI 1.2851 to 5.7542).

Moreover, [8] provided an alternative perspective regarding kidney transplant recipients who have been diagnosed with COVID-19. The study revealed that the usual care Regimen, which includes hydroxychloroquine, led to a reduced overall mortality rate (23%) and ICU mortality rate (23%) compared to a more intensive Regimen comprising hydroxychloroquine and other antivirals such as Remdesivir (overall mortality rate 18%, ICU mortality rate 18%). Nevertheless, the relative risk analysis did not reveal a statistically significant disparity between the two treatment protocols (RR 0.806 for both overall and ICU mortality).

Further research, [9-11], examined the efficacy of a combination therapy consisting of Remdesivir, Tocilizumab, and Methylprednisolone, compared to a control Regimen of Tocilizumab and Methylprednisolone. The group received the intervention had a greater rate of death while in the hospital (18.18%) compared to the control group (8.75%). This finding was also confirmed by the relative risk analysis, which indicated a relative risk of 2.052 with a 95% confidence interval of 0.746-5.645.

Furthermore, [10] employed a distinct methodology by evaluating death rates within the timeframes of 14 and 28 days. The study emphasized the efficacy of Remdesivir, which was linked to a reduced overall mortality at both time intervals in comparison to treatments without Remdesivir. The hazard ratios (HR) for death at 14-day and 28-day intervals were 0.76 (95% confidence interval [CI] 0.69-0.83) and 0.88 (95% CI 0.81-0.96), respectively. These findings indicate that Remdesivir has a beneficial effect in reducing mortality.

Additional contributions, [1, 9], have also made contributions to this body of research by presenting their findings on the death rate within 28 days of hospitalization. One found [9] that the mortality rate was somewhat lower in the group treated with Remdesivir (17.3%) compared to the group not treated with Remdesivir (19.7%). On the other hand, [1] reported a little higher mortality rate in the group treated with both Remdesivir and Dexamethasone (36.5%) compared to the group treated with Dexamethasone alone (29.7%).

In total, these analyses on mortality highlight the intricate nature of handling severe COVID-19 cases and emphasize the crucial significance of choosing the most suitable treatment approach. The study demonstrates the varying effects of several drug combinations, such as Remdesivir, Dexamethasone, Tocilizumab, and Hydroxychloroquine, on patient outcomes. This emphasizes the need to consistently assess and modify treatment protocols based on evolving clinical data.

The exhaustive examination of COVID-19 treatment protocols not only provides insights into the progression of the disease and death rates, but also highlights other important clinical outcomes such as acute kidney failure, rates of patients being discharged from the hospital, admissions to the intensive care unit, the need for mechanical ventilation, requirements for oxygen therapy, usage of extracorporeal membrane oxygenation (ECMO), and the duration of hospital stays. Gaining a comprehensive viewpoint is crucial for comprehending the complete extent of patient care within the context of COVID-19.

Regarding acute renal failure, the research exhibits a combination of positive and negative findings. [7] found that the occurrence of renal failure was much lower in patients who received Remdesivir (2.1%) compared to those who were treated with hydroxychloroquine Regimens (7.9%). This suggests that Remdesivir may have a protective impact on the kidneys. In contrast, [8] found that kidney transplant recipients who were treated with a combination of hydroxychloroquine and antiviral treatments had a greater occurrence of renal failure (50%) compared to those who received conventional care (43%).

The findings suggest that patients treated with Remdesivir have a modestly elevated rate of hospital discharges. According to [6], the discharge rate for patients treated with Remdesivir was 50.85%, whereas it was 44.96% for those not treated with Remdesivir. Similarly,

[9] found that the rate of discharge in the Remdesivir group was 81.7%, which was somewhat higher than the 80.1% rate in the group that did not receive Remdesivir.

Opposing patterns were noted in ICU admissions. [8] revealed a significantly elevated rate of ICU admissions in their intervention group (47%) in comparison to the standard care group (27%). In contrast, another study [6], demonstrated that the group receiving Remdesivir had a decreased rate of admission to the intensive care unit (30.90%) compared to the group not receiving Remdesivir (37.15%).

In the context of mechanical ventilation, [11] found that the intervention group had a larger need for ventilation (27.27%) compared to the control group (11.25%). In contrast, [8] documented a more limited disparity in mechanical ventilation rates between the intervention group (21%) and the control group (24%).

An additional crucial area of emphasis was oxygen therapy. [4] revealed a higher demand for oxygen therapy in the Dexamethasone+Remdesivir group (6.5%) compared to the Dexamethasone-only group (4.0%). [8] found that the intervention group had a significantly higher need for oxygen therapy (84%) compared to the control group (44%).

The ECMO utilization was infrequent, as evidenced by [4], suggesting its application solely in the most critical instances. Finally, the duration of hospital stays differed throughout the research. [7] found that patients treated with Remdesivir had a shorter hospital stay of 18.0 days compared to those treated with hydroxychloroquine, who had a stay of 22.0 days. In contrast, [5, 6] reported average stays of 25.6 days and 14 days, respectively, for groups treated with Remdesivir.

Overall, these investigations emphasize the intricate nature of handling COVID-19, demonstrating how various treatment protocols impact a broad spectrum of clinical results. These insights are crucial for thorough patient treatment, facilitating more knowledgeable and strategic therapeutic decision-making and resource allocation in the on-going fight against COVID-19.

After conducting a thorough examination of nine trials that examined the effectiveness of Remdesivir in treating COVID-19 in real-world settings, the ROBINS-I risk of bias analysis identified varying degrees of bias in different areas. This resulted in a variety of overall risk evaluations, ranging from low to serious (Figure 2).

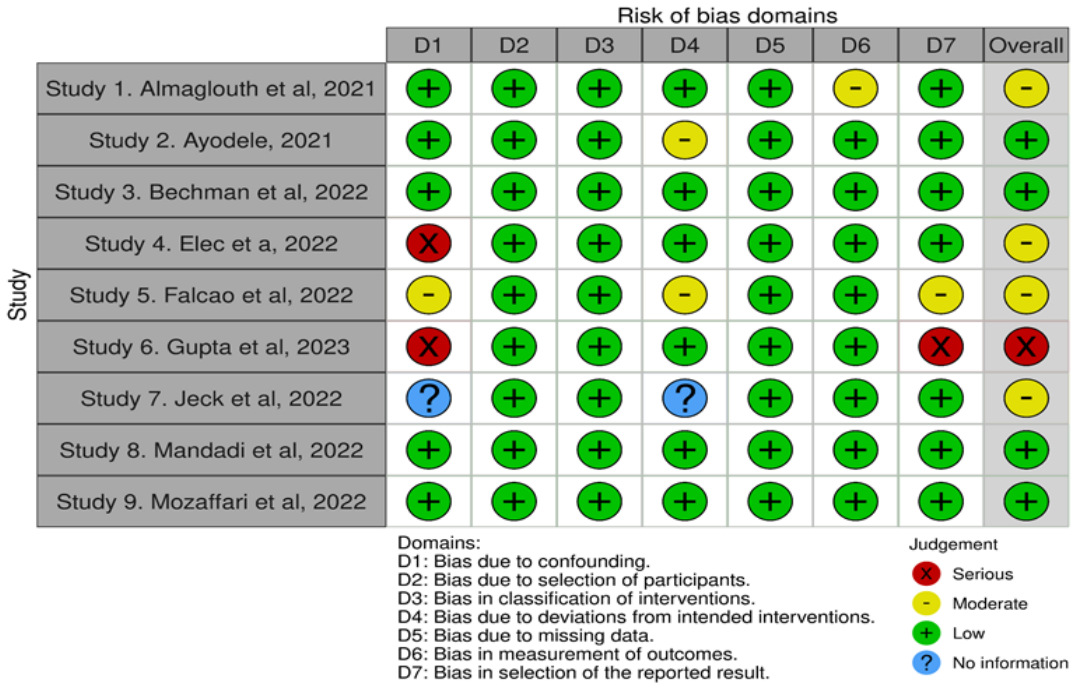


Figure 2: ROBINS-i risk of bias analysis

[4, 11] exhibited a primarily low risk of bias in most areas, suggesting a strong methodology and dependable results. However, [11] revealed a moderate overall risk due to a moderate bias in one specific area.

[1, 9, 10] demonstrated minimal bias across all areas, indicating a high level of scientific rigor and substantial confidence in the findings.

[6, 8] exhibited a moderate level of bias overall. [8] showed a substantial bias in one area but had minimal bias in other areas. On the other hand, [6] lacked information in many domains, undermining its conclusions' credibility.

[7] revealed a moderate level of bias in various areas, resulting in a moderate level of total risk. This suggests reservations regarding some elements of the study's design or implementation that could impact the dependability of its findings.

The study in 2023, [5], revealed a significant risk of bias in two specific areas, resulting in a substantial total risk. This indicates notable methodological constraints that could significantly impact the accuracy of the study's findings.

These findings emphasize the significance of thoroughly assessing the methodological rigor of studies when evaluating the efficacy of therapies such as Remdesivir. The disparity in the likelihood of bias among different studies highlights the necessity for meticulous study design and reporting in order to guarantee dependable and accurate conclusions in clinical research.

The COVID-19 treatment landscape has been under extensive research, with a focus on medications such as Remdesivir. This antiviral drug has demonstrated clinical benefits in animal models and systematic reviews, positioning it as a potentially efficacious treatment against SARS-CoV-2 [12, 13]. Investigating Remdesivir's real-world effectiveness is crucial, and our study aims to contribute valuable insights in this context.

Several studies, [4-6], meticulously analyse the WHO ordinal scale outcomes, emphasizing the substantial impact of Remdesivir and Tocilizumab in reducing symptom severity in real-world scenarios. Variations in patient responses underscore the need for tailored treatment strategies that consider the unique characteristics of each patient [14].

Remdesivir's pivotal role in influencing mortality outcomes is underscored by various studies. A [15] conducted a randomized controlled trial, revealing a median recovery time of 10 days compared to 15 days in the placebo group. [16] reported a statistically significant 17% reduction in inpatient mortality among patients treated with Remdesivir. [17] conducted a systematic review and meta-analysis, indicating lower mortality risk and hastened clinical recovery associated with Remdesivir. The findings are consistent with the study in 2020, [18], that showed mortality benefits within 14 days of Remdesivir administration. [19] highlighted the association of early Remdesivir administration with higher recovery rates and lower need for ICU admission.

Studying the influence of patient characteristics, especially age and comorbidities, on Remdesivir outcomes is crucial. [5] included a retrospective analysis, revealing a significant correlation between age and Remdesivir outcomes, with a lower mortality rate observed in patients below 60 years old. Also, [20] emphasized the impact of age and comorbidities on the clinical outcomes of critically ill COVID-19 patients receiving Remdesivir. In addition, another study [21] examination of disease severity in the context of Remdesivir treatment illuminated more pronounced benefits among patients with moderate disease compared to those with severe illness.

Our systematic and narrative review, drawing evidence from studies [22-24], sheds light on critical clinical implications of Remdesivir in treating COVID-19 in real-world settings. The evidence underscores the pivotal role of Remdesivir in influencing patient outcomes, emphasizing the need for healthcare practitioners to tailor treatment strategies based on patient characteristics, disease severity, and comorbidities. The observed age-dependent response, differential efficacy based on disease severity, and the impact of comorbidities necessitate a nuanced approach to treatment planning.

In our comprehensive review of the real-world effectiveness of Remdesivir in COVID-19, it is imperative to acknowledge the inherent limitations within the included studies. The retrospective designs employed in [1, 5, 7-11, 21] introduced a degree of inherent bias and limitations in establishing causation. Variations in study populations further complicate the interpretation of findings, urging caution in the generalization of results to diverse clinical scenarios.

While our systematic review aims for inclusivity, it is crucial to discuss potential biases within the selected studies. Variability in methodologies, patient selection criteria, and reporting mechanisms may introduce biases that impact the robustness of our conclusions. Addressing these limitations transparently enhances the validity of our findings and guides practitioners in interpreting the results judiciously.

To propel the field forward, our discussion extends to future research directions. Recognizing the current gaps, we advocate for more observational studies and real-world evidence collection to provide a comprehensive understanding of Remdesivir's effectiveness. Long-term follow-ups are essential to discern the sustained efficacy and potential late-emerging effects of Remdesivir. Further investigations into specific patient subgroups, concerning age, comorbidities, and disease severity, will refine our understanding and facilitate targeted therapeutic strategies.

Our systematic and narrative review makes substantial contributions to the evolving literature on COVID-19 treatment efficacy, particularly in the context of Remdesivir in real-world scenarios. By synthesizing findings from the included studies, we offer a comprehensive overview that aids in distilling valuable insights for clinicians and researchers alike.

The studies included in our review provide unique insights, contributing significantly to the understanding of the real-world effectiveness of Remdesivir in the dynamic nature of COVID-19 management. Study of age-related variations [8], exploration of comorbidity impacts [11], and examination of disease severity [10] enhance our collective knowledge, paving the way for more informed decision-making in the clinical setting. Equipped with a nuanced understanding of Remdesivir's real-world effectiveness in COVID-19 treatment, our review serves as a valuable guide for healthcare practitioners navigating the complexities of clinical decision-making. The age-dependent response, influence of comorbidities, and disease severity considerations highlighted in our review empower clinicians to tailor interventions based on individual patient profiles. The evidence-based insights provided contribute to enhanced patient care and improved outcomes.

Conclusion

To sum up, Remdesivir stands as a significant agent in COVID-19 treatment, its real-world effectiveness supported by substantive real-world evidence. Despite the limitations of individual studies, our systematic and narrative review delivers crucial guidance for evidence-based practice in the fight against COVID-19.

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