Title: The safety and efficacy of remdesivir-dexamethasone combination therapy versus dexamethasone monotherapy in COVID-19: A rapid review and meta-analysis

Faranak Salajegheh[1], Nasir Arefinia[2*], Zohreh-al-sadat Ghoreshi[2], Mohsen Nakhaie[3,4], Mohammad Rezaei Zadeh Rukerd[3], Javad Charostad[4]

1. Clinical Research Development Unit, School of Medicine, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

2. Student Research Committee Jiroft University of Medical Sciences, Jiroft, Iran

3. Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

4. Department of Microbiology, Faculty of Medicine, Shahid Sadoughi University of Medical Science, Yazd, Iran

Corresponding Author: Javad Charostad, Department of Microbiology, Faculty of Medicine, Shahid Sadoughi University of Medical Science, Yazd, Iran. Tell: +989137554118, Email: j.4ostad@gmail.com, J.Charostad@ssu.ac.ir

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Abstract

The COVID-19 pandemic has had and is expected to continue having, a profound impact on the physical health of individuals at a global scale. This study aimed to evaluate the efficacy and safety of remdesivir in combination with dexamethasone, compared to dexamethasone alone, in the treatment of COVID-19. To achieve this objective, several global databases, including Google Scholar, PubMed, Scopus, Embase, and ISI, were systematically searched in January 2023. Both MeSH terms and relevant keywords were employed in the search strategy. Statistical analyses were conducted using STATA version 15.0 (StataCorp LLC, College Station, TX, USA). The analysis was conducted using a random-effects model. To assess the degree of heterogeneity among the studies, we utilized the chi-squared test and the I^2 index. Publication bias was evaluated through Egger's test and Begg's funnel plots. Finally, a total of nine studies were included in the analysis. The median length of hospitalization for patients treated with dexamethasone, with or without remdesivir, was 9.89 days (interquartile range: 2.65–21) compared to 11 days (interquartile range:

7–19) (p = 0.37), showing no significant difference between the two groups. The mortality rates among patients who received dexamethasone, with or without remdesivir, were 9% (95% CI: 4–14, p = 0.00) and 18% (95% CI: 8–22, p = 0.00), respectively, irrespective of remdesivir use. Ultimately, the combination of Remdesivir and dexamethasone did not shorten hospital stays. Still, it did result in fewer in-hospital fatalities and a lower fatality rate, which may indicate a decrease in the course of the disease.

Keywords: COVID-19, Remdesivir, Dexamethasone, Treatment, Meta-Analysis.

1. Introduction

COVID-19, caused by the highly transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was officially declared a global pandemic by the World Health Organization (WHO) in March 2020 (1) . The global COVID-19 pandemic has resulted in significant loss of life, widespread morbidity, and profound economic disruptions on a global scale (2). Numerous medications, including antiviral drugs, immunomodulatory agents, and other supportive therapies, have been proposed or authorized for the management of COVID-19. However, the urgent need for a consistently effective and safe treatment for COVID-19 remains a critical issue (3).

Remdesivir is a broad-spectrum antiviral drug originally developed for the treatment of Ebola virus outbreaks. Despite its development for Ebola, clinical trials have shown that remdesivir does not provide substantial survival benefits. With the onset of the COVID-19 pandemic, remdesivir emerged as a potential treatment due to its broad-spectrum antiviral activity. Consequently, several clinical trials have been conducted to assess the efficacy and safety of remdesivir for the treatment of COVID-19 (4).

Dexamethasone, a corticosteroid, is primarily used to treat inflammatory and immune-mediated conditions. Its potent anti-inflammatory properties have led to its consideration as a

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potential treatment for COVID-19. In 2020, the landmark RECOVERY trial assessed the efficacy of dexamethasone in treating COVID-19. The study demonstrated that dexamethasone administration significantly reduced mortality risk among COVID-19 patients who required mechanical ventilation or supplemental oxygen (5).

Based on the existing evidence, both remdesivir and dexamethasone, when administered individually, are considered safe and effective treatments for patients diagnosed with COVID-19 (6-8). Nonetheless, the combined use of these drugs should be reserved for patients who specifically require supplemental oxygen or mechanical ventilation. Further research is needed to thoroughly evaluate the safety and efficacy of alternative drug combinations for the treatment of COVID-19 (9).

Several studies have been conducted to assess the safety and efficacy of the remdesivir-dexamethasone combination for the treatment of COVID-19 (9, 10). This manuscript aim is to conduct a comprehensive review of the existing literature, employing a meta-analysis approach, to evaluate the safety and effectiveness of combining remdesivir with dexamethasone compared to dexamethasone alone in the treatment of COVID-19.

2. Methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, we conducted a thorough systematic review of the available evidence and present our findings in this study (11).

2.1. Search strategy

A comprehensive search was conducted to identify and extract published studies that investigated the safety and efficacy of combining remdesivir with dexamethasone compared to dexamethasone alone for the treatment of COVID-19. The search utilized a combination of keywords, including "COVID-19," "SARS-CoV-2," "2019-nCoV," "2019 Novel Coronavirus," "Remdesivir," "Dexamethasone," "pharmacological intervention," and "safety." International databases such as Google Scholar, PubMed, Embase, Scopus, and ISI were thoroughly searched using a combination of the mentioned keywords and Boolean operators ("OR" and "AND"). Furthermore, the reference lists of the extracted studies were examined to identify additional

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papers that could contribute to the review. After completing the search process, the retrieved records were imported into EndNote, a reference management software, for organization and management. Duplicate records were identified and removed.

2.2. Inclusion and exclusion criteria

In our rapid review and meta-analysis, we employed the following inclusion criteria to select studies for analysis: 1) Original articles published in English, and 2) Studies that specifically investigated the use of remdesivir in combination with dexamethasone for the treatment of COVID-19, as opposed to studies focusing on their individual use. We excluded the following: 1) Review articles, editorials, and book chapters, 2) Articles that investigated the use of remdesivir or dexamethasone alone or in combination with other drugs.

The flow diagram visually presents the selection process and illustrates the studies included in our analysis (Figure 1).

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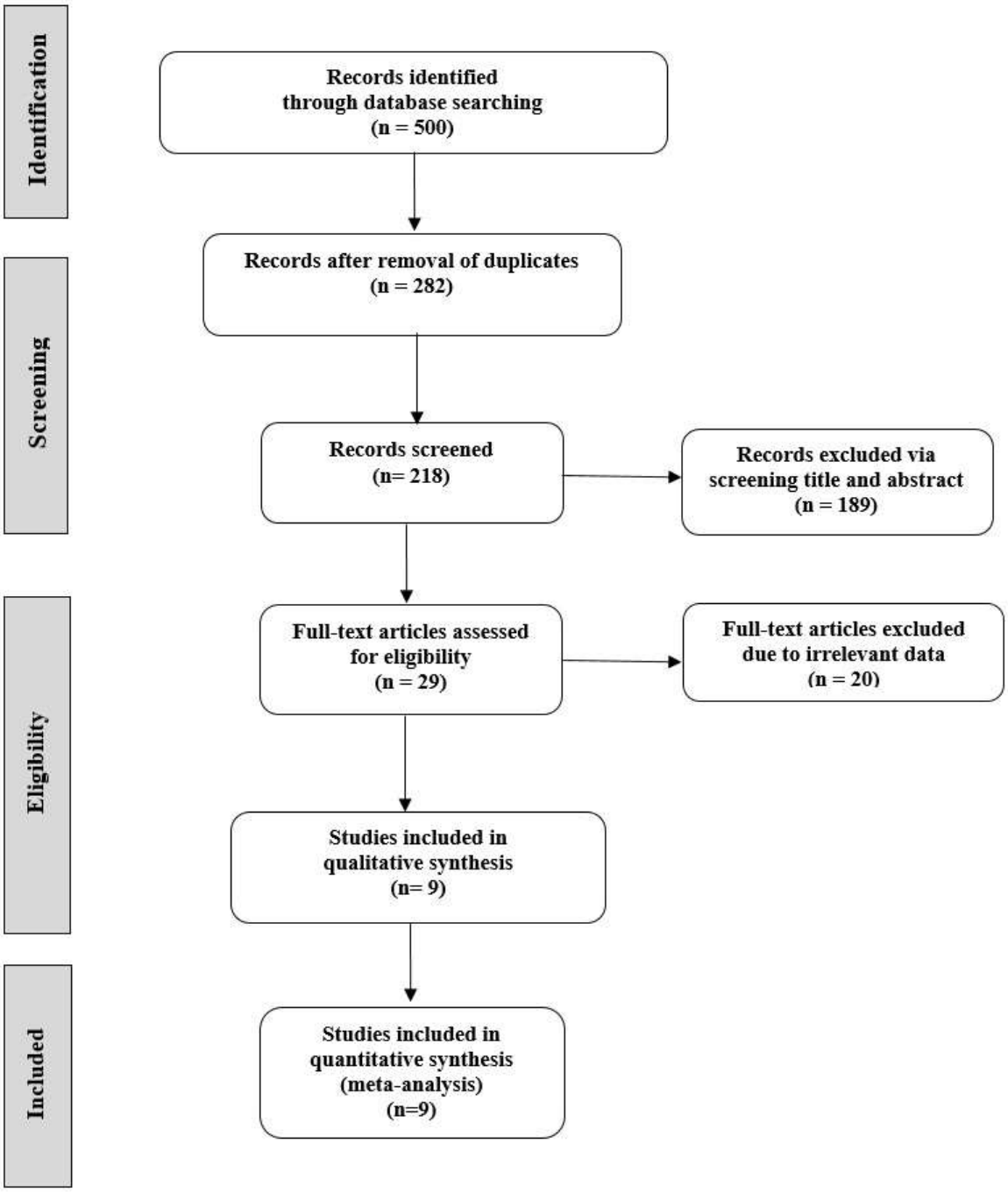

Figure 1. Flow diagram of the study design process.

2.3. Quality assessment and risk of bias evaluation in included studies

To assess the risk of bias in the included studies, we employed the Newcastle-Ottawa Scale (NOS) (12). This scale assigns up to 9 points for case-control and cohort studies, with higher scores indicating better quality and a lower risk of bias. Based on the NOS assessment, the studies were

categorized as follows: studies 1-3 were rated as low quality, studies 4-6 as moderate quality, and studies 7-9 as high quality (Table 1).

Table 1. Risk of bias assessment of the included studies

Study (Reference)	Selection				Comparability	Outcome				
	Exposed representation	Nonexposed selection	Ascertainment of obesity	Outcome absent at study start	Adjustment by age and nodal status or stage	Outcome assessment	Follow-up length	Adequacy of follow-up	Overall score	Quality of study
Marrone A (9)	**1**	**1**	-	**1**	**1**	**1**	**1**	**1**	**7**	High
Alibrahim RS (13)	-	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**7**	High
Ngo DQ (14)	**1**	**1**	-	**1**	**1**	**1**	**1**	**1**	**7**	High
Gressens SB (10)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**8**	High
De Pascale G (15)	**1**	**1**	-	**1**	**1**	**1**	**1**	**1**	**7**	High
Grundmann A (16)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**8**	High
Wong CK (17)	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**8**	High
Yasuda Y (18)	**1**	**1**	-	**1**	-	**1**	**1**	**1**	**6**	Moderate
Benfield T (19)	**1**	**1**	-	**1**	**1**	**1**	**1**	-	**6**	Moderate

2.4. Data extraction

In this study, two independent authors extracted data, including the first author's name, study location, year of publication, sample size, mean age of participants, study design, duration of hospitalization, and mortality rates for patients treated with either remdesivir-dexamethasone combination therapy or dexamethasone alone for COVID-19. Finally, the collected data underwent thorough review by other authors involved in the research to identify and rectify any potential errors or inconsistencies. Subsequently, all authors carefully reviewed and confirmed the accuracy of the data, ensuring its reliability and integrity in the final analysis.

2.5. Risk of bias across studies

To assess publication bias, both the Egger test and Begg's funnel plots were used. A p-value of less than 0.05 was considered indicative of significant publication bias.

2.6. Statistical analysis

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In our analysis, variables such as sample size, mean, and standard deviation were grouped for data analysis. To determine the weight of each study, we used the inverse variance method, which assigns higher weights to studies with smaller variances (greater precision) and lower weights to those with larger variances (lower precision). Heterogeneity among the studies was assessed using the Q test and I^2 index, with a significance level of less than 10%. The random-effects model was employed to analyze the heterogeneous data, and all analyses were performed using STATA 15.0 software.

3. Results

In our study, nine studies were included (9, 10, 13-19). Among these patients, 13,712 received the remdesivir-dexamethasone combination therapy, while 22,382 patients received dexamethasone alone. Table 2 presents an overview of the main characteristics of the included studies, such as the first author's name, country, publication year, study design, total sample size, mean age of participants, duration of hospitalization, and mortality rates of patients treated with remdesivir-dexamethasone combination.

Table 2. characterizations of articles reviewed in the present study

Author's name	Country	Year	Study design	Total Sample size of study	Age	Hospitalization (Days)	Mortality
Marrone A (9)	Italy	2022	Prospective quasi-experimental study	151	64 (remdesivier-dexamethasone group) 66 (dexamethasone group)*	13 (remdesivier-dexamethasone group) 17 (dexamethasone group)*	1.3% (remdesivier-dexamethasone group) 16% (dexamethasone group)
Alibrahim RS (13)	Qatar	2022	retrospective cohort study	133	56*	-	8.3%
Ngo DQ (18)	USA	2022	Retrospective Study	191	63*	13.31 (remdesivier-dexamethasone group)	-

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Gressens SB (10)	France	2022	retrospective multicenter study	325	68	9 (remdesivier-dexamethasone group) 9 (dexamethasone group)	9% (remdesivier-dexamethasone group) 18% (dexamethasone group)
De Pascale G (17)	Italy	2022	Prospective cohort study	132	64	21 (remdesivier-dexamethasone group)	10.6% (remdesivier-dexamethasone group)
Grundmann A (14)	UK	2022	Prospective cohort study	89297	60 (remdesivier-dexamethasone group from day 1) 68 (dexamethasone group)*	17 (remdesivier-dexamethasone group) 17 (dexamethasone group)*	16% (remdesivier-dexamethasone group from day 1) 28% (dexamethasone group)
Wong CK (15)	China	2021	territory-wide cohort	10445	?	3	7.7% (remdesivier-dexamethasone group) 11.6% (dexamethasone group)
Yasuda Y (16)	Japan	2022	single-center, retrospective study	90	70.5 ± 1.9 (remdesivier-dexamethasone group)	Remdesivir and dexamethasone group: 13 days (among patients aged 65 years or older) and 6 days (among patients younger than 65 years)	5% (remdesivier-dexamethasone group)
Benfield T (19)	Denmark	2021	Two population-based nationwide cohorts	2747	71 (February-May); 69 (June-December)	-	12.6% (remdesivier-dexamethasone group)

Note: * indicates the median value in each respective cell.

3.1. Hospitalization days and the mortality rate

The median duration of hospitalization in treatment with dexamethasone, with or without remdesivir, was 9.89 (IQR: 2.65–21) and 11 (IQR: 7–19) days, respectively ($p = 0.37$). Moreover,

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the mortality rates of patients who received dexamethasone, with or without remdesivir, was 9% (95% CI: 4–14, $p = 0.00$) and 18% (95% CI: 8–22, $p = 0.00$), correspondingly (Figure 2 & 3).

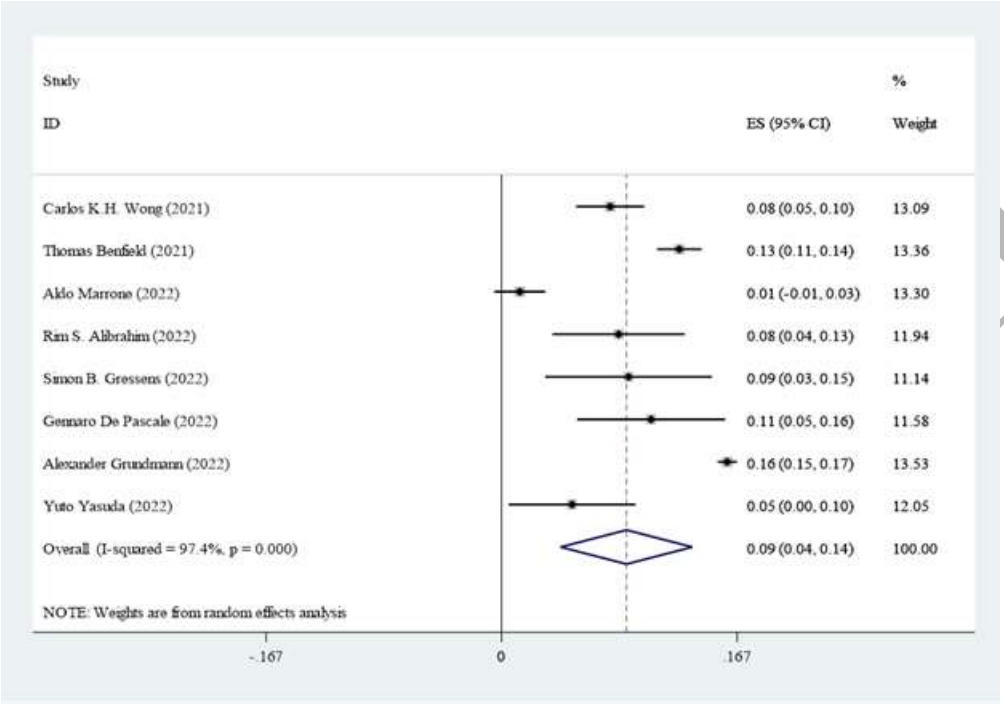

Figure 2. The overall estimate of the mortality rate of patients in treatments with remdesivir and dexamethasone in the investigated studies with 95% CI (based on a random model).

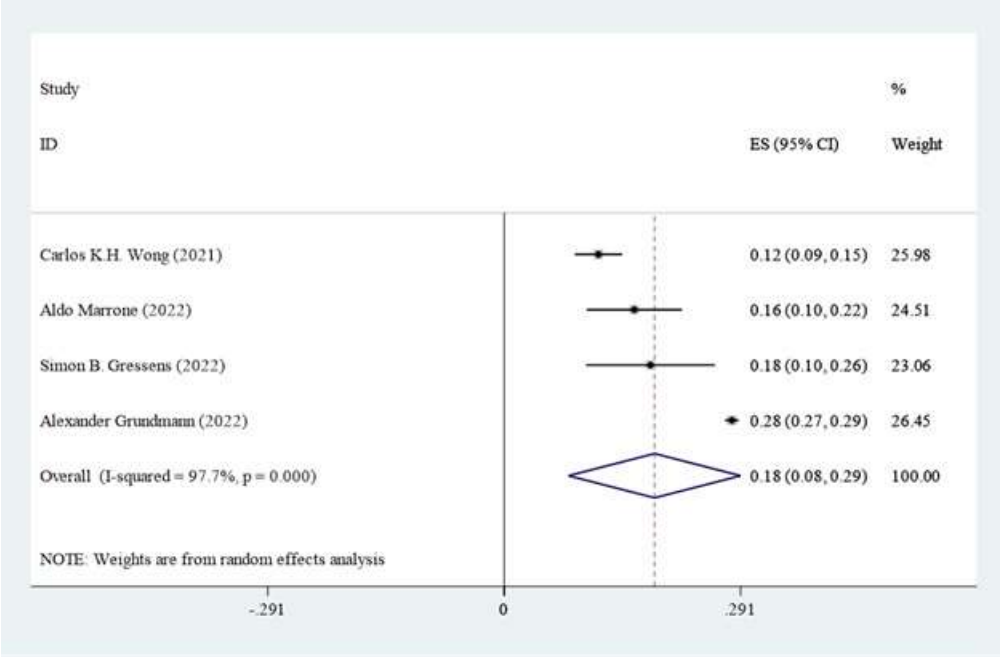

Figure 3. The overall estimate of the mortality rate of patients in treatments with dexamethasone in the investigated studies with 95% CI (based on a random model).

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3.2. Clinical improvement

The study conducted by Marrone et al. (2022) reported significant differences in viral clearance between the remdesivir-dexamethasone group and the dexamethasone alone group. The remdesivir-dexamethasone group achieved faster viral clearance, with a median clearance time of 6 days compared to 16 days in the dexamethasone alone group ($p < 0.001$). At the 6-day mark after treatment initiation, 69% of patients in the remdesivir-dexamethasone group had cleared the virus, while only 20% in the dexamethasone alone group had achieved viral clearance ($p < 0.001$). These results suggest that the combination therapy may be more effective in promoting faster viral clearance. Additionally, patients in the remdesivir-dexamethasone group experienced a rapid and significant decrease in C-reactive protein (CRP) levels by the end of the treatment, which was not observed in the dexamethasone alone group. At the conclusion of treatment, 50.6% of patients in the remdesivir-dexamethasone group had achieved normal respiratory function, compared to only 22.9% in the dexamethasone alone group ($p < 0.0005$) (9).

Gressens et al. examined hospitalized COVID-19 patients receiving low-flow oxygen and dexamethasone. Their study found that adding remdesivir to the treatment regimen did not result in shorter hospitalization or reduced in-hospital mortality rates. However, the combination of remdesivir and dexamethasone appeared to have a beneficial effect on the combined outcome of death and transfer to the intensive care unit (10).

The study by De Pascale et al. yielded several key findings regarding the use of Rem-Dexa (remdesivir-dexamethasone) for COVID-19 treatment: 1) The 28-day intubation rate was significantly lower in the Rem-Dexa group compared to the control group (19.7% vs. 48.5%, $p < 0.01$), suggesting that the combination therapy may reduce the need for intubation among COVID-19 patients, and 2) Although clinical improvement at the end of treatment was greater in the Rem-Dexa group compared to the control group (69.7% vs. 51.5%, $p = 0.05$), there were no significant differences in 28-day or 90-day mortality rates between the groups. The 28-day mortality rates were 4.5% for the Rem-Dexa group and 15.2% for the control group ($p = 0.08$), and the 90-day mortality rates were 10.6% for the Rem-Dexa group and 16.7% for the control group ($p = 0.45$) (17).

The study by Grundmann et al. assessed the impact of various treatment approaches on neurological complications and mortality in patients with severe COVID-19. The key findings are

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as follows: Treatment with dexamethasone, remdesivir, and their combination was associated with lower frequencies of neurological complications, with odds ratios (OR) of 0.76 (95% CI = 0.69–0.83), 0.69 (95% CI = 0.51–0.90), and 0.54 (95% CI = 0.47–0.61), respectively. The combined treatment of remdesivir and dexamethasone also led to a significant reduction in mortality (OR = 0.67, 95% CI = 0.63–0.71), suggesting a synergistic effect, as indicated by log(0.67) < [log(0.86) + log(0.97)] (14).

The study by Wong et al. found that the remdesivir-dexamethasone group had a 2.65-day shorter hospital length of stay among survivors, lower WHO clinical progression scale scores from five days of follow-up onwards, and reduced risks of in-hospital death (HR = 0.59, 95% CI = 0.36–0.98, p = 0.042) and composite outcomes. Additionally, there was no increased risk of acute respiratory distress syndrome (ARDS) associated with the combination therapy (15).

4. Discussion

Our study aimed to evaluate the safety and efficacy of remdesivir-dexamethasone combination therapy compared to dexamethasone monotherapy in COVID-19 treatment. The results indicate that there was no significant difference in the median duration of hospitalization between the two treatment groups, suggesting that adding remdesivir to dexamethasone did not substantially impact the length of hospital stay. However, mortality rates differed between the groups, with a mortality rate of 18% in the dexamethasone-only group and 9% in the dexamethasone-plus-remdesivir group. This suggests that the addition of remdesivir may have positively influenced mortality outcomes in COVID-19 patients.

The CoDEX trial, a randomized, double-blind, placebo-controlled study, assessed the safety and effectiveness of dexamethasone in COVID-19 patients requiring supplemental oxygen but not mechanical ventilation. Firstly, dexamethasone treatment was associated with a significant reduction in mortality compared to the placebo group, indicating its beneficial effect on survival in these patients. Lastly, the dexamethasone group experienced a higher rate of ventilator-free days compared to the placebo group, suggesting that dexamethasone facilitated faster recovery and reduced the need for mechanical ventilation. These results underscore the potential benefits of dexamethasone in managing COVID-19 patients who require supplemental oxygen (20).

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A recent meta-analysis of fourteen randomized controlled trials comprehensively evaluated the efficacy of corticosteroids, including dexamethasone, in treating COVID-19. The findings demonstrated a significant reduction in mortality among COVID-19 patients requiring supplemental oxygen or mechanical ventilation when treated with corticosteroids. The pooled analysis revealed a consistent and notable benefit of dexamethasone in improving survival outcomes for patients with more severe disease manifestations. This suggests that corticosteroids play a crucial role in reducing mortality rates and enhancing patient outcomes in this population (21).

Several studies have investigated the safety and effectiveness of combining remdesivir with dexamethasone for treating COVID-19. One notable example is the DisCoVeRy trial, a randomized, open-label study designed to evaluate this combination therapy. The results indicated that combining remdesivir with dexamethasone led to significant improvements in patient outcomes compared to standard care. Firstly, the combination therapy was associated with a notable reduction in the time to recovery, suggesting a quicker resolution of COVID-19 symptoms and overall health improvement. Lastly, the trial demonstrated a significant reduction in mortality rates among patients receiving the combination therapy compared to those receiving standard care alone. This suggests that the synergistic effect of these medications may enhance disease management and improve patient survival (22).

The Adaptive COVID-19 Treatment Trial 2 (ACTT-2) was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of remdesivir combined with dexamethasone in COVID-19 patients requiring supplemental oxygen but not mechanical ventilation. The results demonstrated that this combination therapy significantly reduced the time to recovery compared to both placebo and dexamethasone alone. This suggests that the combination of remdesivir and dexamethasone can enhance clinical outcomes for COVID-19 patients, particularly those needing supplemental oxygen. The trial supports the use of both medications as part of the treatment strategy for such patients (23).

Finally, a network meta-analysis (NMA) was conducted to evaluate the effectiveness of remdesivir in hospitalized COVID-19 patients requiring supplemental oxygen. The findings indicated that, compared to best supportive care, remdesivir is expected to improve outcomes such as reduced mortality risk, enhanced recovery rates, and decreased dependence on oxygen support

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for patients requiring either any oxygen or low-flow oxygen (LFO2) during hospitalization for COVID-19 (24).

This study has some strength and limitation. One of the key strengths is the inclusion of a large patient cohort, allowing for robust comparisons between remdesivir-dexamethasone combination therapy and dexamethasone monotherapy. Additionally, the systematic search and inclusion of studies from multiple countries enhance the generalizability of the findings. However, the study has limitations, such as the variability in study designs and patient populations across the included studies, which could introduce heterogeneity. Furthermore, while the analysis demonstrates the potential benefit of reduced mortality, the lack of significant impact on hospitalization duration warrants further investigation to clarify the specific role of remdesivir in combination therapy. Lastly, this study was unable to fully evaluate the safety profile of the remdesivir-dexamethasone combination due to insufficient detailed safety data across the included studies, highlighting the need for more comprehensive safety assessments in future research.

In conclusion, while the combination of dexamethasone and remdesivir did not significantly reduce the duration of hospitalization in patients with COVID-19 pneumonia, it was associated with a decreased mortality rate and a potential reduction in disease progression, as indicated by fewer in-hospital deaths. Further research is required to elucidate the specific contribution of remdesivir to these observed clinical effects.

Abbreviations

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS: Newcastle-Ottawa Scale; CRP: C-reactive protein; ARDS: Acute respiratory distress syndrome; ACTT-2: Adaptive COVID-19 Treatment Trial 2; NMA: Network meta-analysis; LFO2: Low-flow oxygen.

Declarations

Acknowledgment

None.

Data availability

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Not applicable.

Ethical approval and consent to participate

Ethical approval was not required for this study because this study is a meta-analysis.

Conflicts of Interest

We declare no conflicts of interest regarding our paper.

Authors' contributions:

J.C. and F.S. contributed to study conception, design, and analysis. N.A. and Z.G. wrote the draft version of the manuscript. M.N. and M.R.Z.R. contributed to collection and data analysis. All authors read and approved the final version of the manuscript.

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