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Efficacy of Remdesivir on Clinical Outcomes in COVID-19 Patients: A Study in a Tertiary Care Hospital in Pakistan

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Abstract

Background: **As of October 3, 2023, the global COVID-19 case tally exceeded 696 million, with almost 7 million fatalities. Remdesivir, approved for treatment of COVID-19 by regulatory bodies, has seen varying recommendations by the World Health Organization over time. Despite certain studies questioning its efficacy, others highlight potential benefits. The objective of this study was to gauge the impact of remdesivir on clinical outcomes in a Pakistani tertiary care hospital.**

Methods: **An analytical cross-sectional study was conducted on 108 COVID-19 patients at Mayo Hospital Lahore between September 2020 and August 2021. Of these, 52 received remdesivir. The study employed a structured proforma for data collection, with analyses conducted using SPSS version 26, considering a p-value of less than 0.05 as statistically significant.**

Results: **Demographic distribution between remdesivir-treated and untreated groups was similar. Significant improvement was observed in the remdesivir cohort in terms of oxygen saturation (58%), ferritin levels (58.2%), chest X-ray results (67.8%), and discharge rates (66.7%) when compared to the untreated group. Stratification based on disease severity showed that remdesivir was particularly beneficial for moderate illness cases in several parameters.**

Conclusion: **This study suggests that remdesivir can be associated with improved outcomes, especially in patients with moderate COVID-19 severity. The data emphasizes the importance of the disease stage when considering therapeutic interventions and calls for more region-specific research to guide health responses amid diverse epidemiological landscapes.**

Keywords: COVID-19, Remdesivir, Tertiary care hospital, Clinical outcomes, Mortality rates, Antiviral treatment, Pakistan

1. Introduction

By October 3, 2023, the world has witnessed an alarming 696,120,461 confirmed cases of COVID-19 and 6,922,780 resultant fatalities.[1] In a significant declaration, the Director-General of the World Health Organization (WHO) elucidated that while COVID-19 remains a prevailing health challenge, it has transitioned from being a public health emergency of international concern (PHEIC) to an enduring health issue.[2]

Remdesivir, characterized as a nucleotide prodrug of an adenosine analog, has exhibited both in vitro and in vivo efficacy against the SARS-CoV-2 virus.[3] This has led to its approval by the Food and Drug Administration (FDA) and The Drug Regulatory Authority of Pakistan (DRAP) for treating COVID-19 in adults as well as pediatric patients aged 28 days or older and with a weight of at least 3 kg.[4,5] For those non-hospitalized patients exhibiting mild to moderate COVID-19 symptoms but being at an elevated risk of evolving into a severe disease phase,

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the initiation of remdesivir within the first 7 days from symptom emergence is recommended, with a suggested treatment duration of 3 days. For those admitted to a hospital, the recommended treatment period with remdesivir spans 5 days, or it continues up to the point of discharge, depending on which transpires first.

Despite this, the World Health Organization introduced a conditional recommendation against administering remdesivir to hospitalized patients.[6] This stance stemmed from the lack of conclusive evidence demonstrating remdesivir's capability to enhance survival rates and other patient outcomes, irrespective of disease severity. However, after evaluating new clinical trial data released on April 22, 2022, regarding hospital admission outcomes, WHO updated its guidance to recommend the use of remdesivir for mild to moderate COVID-19 patients who have an increased risk of being hospitalized.[6]

In a clinical study from China employing a randomized, double-blind, placebo-controlled methodology, no substantial clinical advantages were discerned in severe COVID-19 patients treated with remdesivir.[7] Conversely, another trial conducted in 60 sites across the world with a similar design discovered a reduced recovery duration in hospitalized COVID-19 patients given remdesivir.[8] A subsequent study in the U.S. indicated that a 5-day regimen of remdesivir yielded a marked improvement in clinical conditions compared to conventional care among those with moderate COVID-19 symptoms.[9]

In Sweden, researchers delved into remdesivir's impact on the viral kinetics of SARS-CoV-2 and consequent mortality in patients diagnosed with COVID-19.[10] The findings posited that the drug did not notably alter the span of SARS-CoV-2 viremia, the trajectory of serum viral depletion, the 60-day mortality rate, or any associated adverse hospital events in those exhibiting symptoms for 10 days or fewer upon admission. However, there was a suggestive shortening in viremia duration for a specific subset: those presenting symptoms for 7 days or less upon hospital entry.

An in-depth retrospective review of a hospital patient database in India focusing on COVID-19 revealed that remdesivir was predominantly well tolerated, showcasing a satisfactory safety track record.[11] Notably, 84% of the patients exhibited signs of recovery or improvement, particularly in those below 60 years of age and those administered standard low-flow oxygen.

The aim of this study is to evaluate the impact of remdesivir on clinical outcomes, including symptom alleviation, recovery duration, and overall prognosis in COVID-19 patients admitted to a tertiary care hospital in Pakistan. Existing literature presents a spectrum of findings regarding remdesivir's efficacy in treating COVID-19, with studies from various regions offering differing results. This study, focusing on a tertiary care hospital in Pakistan, aims to add a unique, region-specific dimension to the current body of knowledge. Given the diverse epidemiological patterns, healthcare infrastructures, and patient profiles worldwide, this research offers insights into remdesivir's effectiveness within the specific context of Pakistan's healthcare system.

2. Methods

Ethical approval was obtained from the Institutional Review Board of King Edward Medical University (approval letter: 928/RC/KEMU). The study spanned from September 2020 to August 2021. The participant pool consisted of patients admitted to Mayo Hospital Lahore with PCR-confirmed COVID-19, irrespective of their age and gender. From this pool, we excluded those who received an incomplete course of remdesivir and those in critical condition (defined by specific clinical signs, including a respiratory rate over 30 breaths per minute, oxygen saturation below 94%, and lung infiltrates over 50%, as shown on radiographs).[12,13]

After ensuring adherence to the sample selection criteria and obtaining informed consent, we enrolled a total of 108 participants. Of these, 52 were administered remdesivir, while the remaining 56 received usual care (admission to hospital, contact and droplet precautions, paracetamol for fever, avoidance of ibuprofen/NSAIDs, oral or IV hydration as needed, oxygen administration to maintain saturation >92%, and specific antiviral treatment with Hydroxychloroquine or Chloroquine).[14] Researchers were not directly involved in treatment decisions for patients. For our study, a complete dose of remdesivir was defined as an initial intravenous (IV) bolus of 200 mg, followed by 100 mg IV administered once daily over the subsequent four days.

Data collection employed a structured proforma that captured essential details, including age, gender, presenting symptoms, illness severity, and clinical outcomes. Additionally, SpO 2 measurements were recorded, with particular attention given to drops in saturation or observed improvements. Comprehensive laboratory investigations, such as markers like CRP, ferritin, and D-dimer, were consistently noted. Furthermore, chest

radiographs were taken on days 1 and 5 of hospital admission, with the results categorized into either 'improved' or 'not improved' based on radiological findings.

For data analysis, we used SPSS v.26 and R version 4.3.2. The Chi-square test was applied to discern differences between the cohorts - those who administered remdesivir and those who were not. We further stratified our data based on disease severity.

We employed the prop.test function from the stats package in R to calculate the 95% confidence intervals for the proportions of patients with each clinical outcome. Subsequently, forest plots were generated using the ggplot 2 package to visualize the distribution of clinical outcomes across different stages of illness.

The 95% confidence intervals for the clinical outcomes were calculated using the Wilson score interval method for binomial proportions.[15] This method was chosen due to its robustness for small sample sizes and its ability to provide accurate confidence intervals even when the proportion approaches 0 or 1. The formula used to calculate the 95% CI for each proportion $\hat{p}$ (number of events divided by sample size) is as follows:

$$\text{Lower bound} = \frac{\hat{p} + \frac{z^2}{2n} - z\sqrt{\frac{\hat{p}(1-\hat{p})}{n} + \frac{z^2}{4n^2}}}{1 + \frac{z^2}{n}}$$

$$\text{Upper bound} = \frac{\hat{p} + \frac{z^2}{2n} - z\sqrt{\frac{\hat{p}(1-\hat{p})}{n} + \frac{z^2}{4n^2}}}{1 + \frac{z^2}{n}}$$

Where:

- z is the Z-score corresponding to the desired confidence level (e.g., 1.96 for a 95% CI).
- n is the sample size.

Throughout our analysis, we deemed a p-value of less than 0.05 as indicative of statistical significance.

3. Results

Among the 108 patients enrolled in the study, 52 were administered remdesivir. The mean age of participants was 56.44 ± 14.95 years. This initial demographic and clinical presentation, including age distributions, gender, primary symptoms, and illness severity, are comprehensively detailed (Table 1).

Clinical outcomes and investigative results further emphasized the efficacy of remdesivir (Fig. 1). A significant proportion of patients treated with remdesivir, 58%, displayed improved oxygen saturation (SpO 2) levels, a marked difference when juxtaposed with the 42.0% in the non-remdesivir cohort ($P < 0.001$). Likewise, ferritin levels revealed a similar pattern; 58.2% of patients on remdesivir showed enhanced levels, contrasting with the 41.8% in the untreated group ($P = 0.007$). In terms of radiological outcomes, chest X-ray findings for 67.8% of those in the remdesivir group indicated notable improvement, a stark contrast to the 32.2% in the untreated group ($P < 0.001$). Furthermore, from a clinical outcome perspective, a significant 66.7% of the remdesivir cohort were discharged, a figure substantially higher than the 33.3% observed in the non-remdesivir group ($P < 0.001$). However, it is noteworthy that D-dimer levels did not exhibit any substantial variance between the two groups (Supplementary Table 1).

When data was stratified based on the severity of illness using three-way cross tabulation with the chi-square test, the results provided distinct insights. For patients categorized with moderate illness, marked differences emerged in the treatment outcomes (Fig. 2). Specifically, SpO 2 levels, ferritin levels, chest X-ray findings, and clinical outcomes all showed statistically significant improvements in the remdesivir cohort, with P values being 0.016, 0.023,

Table 1. Characteristics of patients grouped by remdesivir treatment status.

Variables	Category	Total (n = 108)	Remdesivir Group (n = 52)	Usual Care Group (n = 58)
Age	<60	66 (61.1%)	36 (54.5%)	30 (45.5%)
	>60	42 (38.9%)	16 (38.1%)	26 (61.9%)
Gender	Female	31 (28.7%)	16 (51.6%)	15 (48.4%)
	Male	77 (71.3%)	36 (46.8%)	41 (53.2%)
Presenting Complaints	Fever	1 (0.9%)	0 (0.0%)	1 (100%)
	Fever & Cough	59 (54.6%)	37 (62.7%)	22 (37.3%)
	Fever, Cough & SOB	48 (44.4%)	15 (31.2%)	33 (68.8%)
Stage of Illness	Mild	9 (8.3%)	7 (77.8%)	2 (22.2%)
	Moderate	42 (38.9%)	26 (61.9%)	16 (38.1%)
	Severe	57 (52.8%)	19 (33.3%)	38 (66.7%)

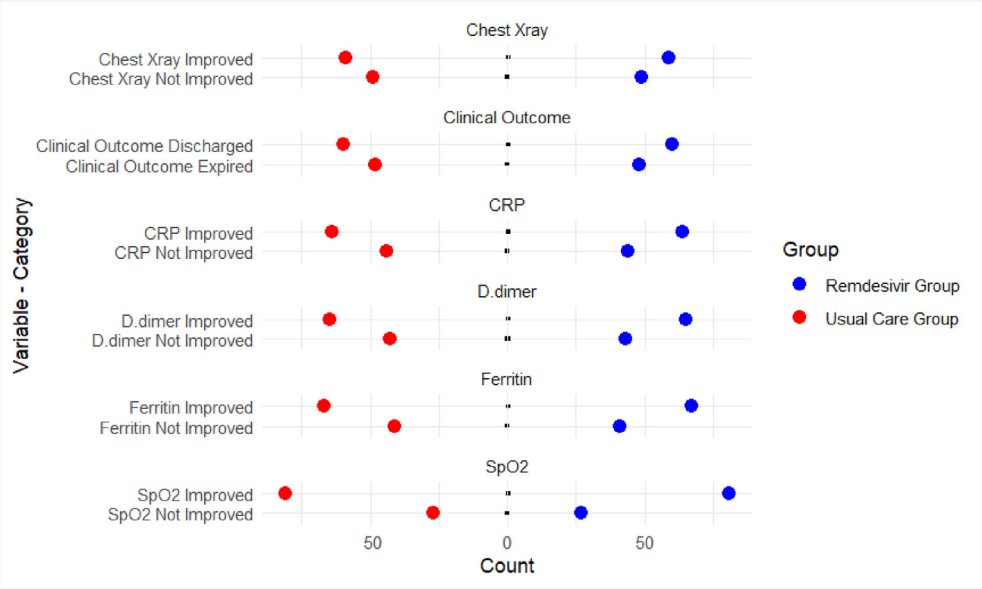

Fig. 1. Forest plot comparison of clinical outcomes between remdesivir and usual care treatment groups across different disease severity levels.

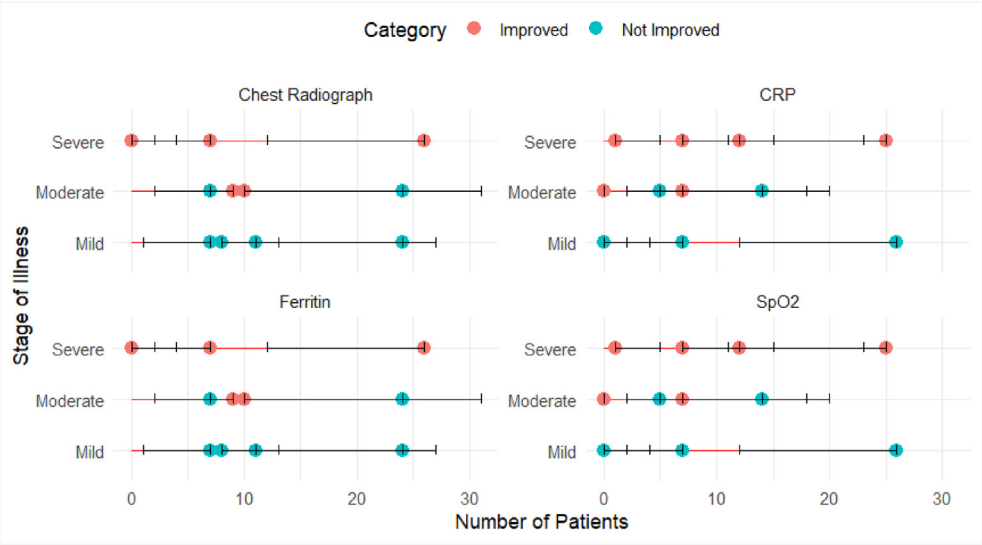

Fig. 2. Forest plot of clinical outcomes for chest radiograph, CRP, ferritin, and SPO2.

0.025, and 0.008 respectively. Notably, CRP levels did not follow this trend, showing any significant difference between the remdesivir and non-redeliver groups. Among patients with severe symptoms, only chest X-ray improvements reached statistical significance with a P value of 0.022. Other parameters in this severity category did not exhibit notable variances. Due to the limited sample size, outcomes for mild illness cases were not computable (Supplementary Table 2).

This forest plot illustrates the clinical outcomes of patients who received remdesivir compared to those who received usual care across different stages of illness for variables including chest Radiograph, CRP, ferritin, and SpO 2. The number of patients discharged and expired are shown for each category, with error bars representing the 95% confidence intervals for the usual care group. The plot demonstrates variations in clinical outcomes between the two treatment groups across these specific variables.

Fig. 3 illustrates the clinical outcomes (i.e., discharged or expired) of patients who received Remdesivir compared to those who received usual care across different stages of illness:

Mild Illness: In the Remdesivir Group, 7 patients were discharged, while 2 patients were discharged

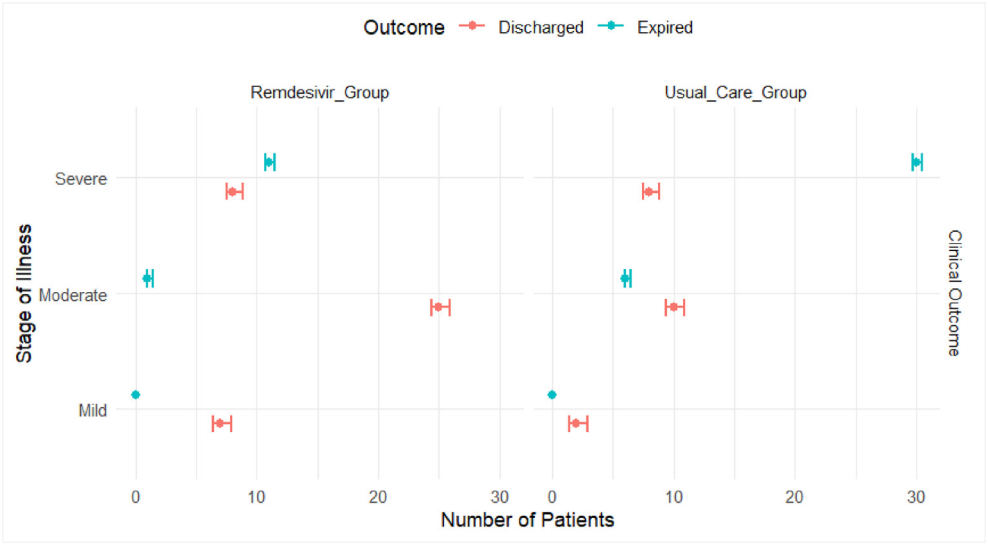

Fig. 3. Forest Plot with 95% CI Showing Clinical Outcomes in Patients Receiving Remdesivir vs. Usual Care. *Blue circles represent patients discharged. Red circles represent patients expired. Error bars indicate the 95% confidence intervals for the number of patients in the Usual Care Group.*

in the Usual Care Group. No patients expired in either group (P=NE).

Moderate Illness: In the Remdesivir Group, 25 patients were discharged, and 1 patient expired. In contrast, 10 patients were discharged, and 6 patients expired in the usual care group (P = 0.008).

Severe Illness: In the Remdesivir Group, 8 patients were discharged, and 11 patients expired. Similarly, 8 patients were discharged, and 30 patients expired in the usual care group (P = 0.95).

Overall, the forest plot indicates a higher number of patients discharged in the Remdesivir Group across all stages of illness compared to the Usual Care Group, with significant variations observed in the number of expired patients.

4. Discussion

While the widespread health concerns due to COVID-19 have persisted, the medical community has diligently sought effective therapeutic interventions. Among the various antiviral agents under investigation, remdesivir garnered attention due to its promise in early laboratory studies.[16] Our research findings highlight the therapeutic potential of remdesivir, particularly as evidenced by the marked improvement in SpO 2 levels among recipients. Importantly, patients manifesting moderate symptoms exhibited superior responses to remdesivir, consistent with literature advocating its use in oxygen-dependent cohorts.[17-20] Nevertheless, some research remains inconclusive about its efficacy in such patient groups.[21]

Moreover, our analysis revealed enhancements in specific laboratory parameters, including CRP, Ferritin, and radiographic changes consistent with chest X-ray findings. Stratification by disease stage elucidated significant therapeutic outcomes for those at the moderate illness phase, particularly concerning ferritin levels. However, our data did not yield any statistical significance for CRP across varying illness stages. This underlines the potential utility of inflammatory markers and radiological indicators as crucial determinants of disease severity and progression.[22] While one investigation identified clinical benefits post a 5-day remdesivir regimen, it failed to highlight any consequential alterations in inflammatory markers.[23] Conversely, another study posited that clinical amelioration post remdesivir administration correlates with improved inflammatory indices, suggestive of disease resolution.[24]

Considering clinical outcomes, a substantial fraction of remdesivir recipients experienced recovery, ultimately leading to hospital discharge.[11] This observed trend was particularly pronounced in the moderate disease category, implicating remdesivir's enhanced efficacy at this stage. However, the drug's potential seemed limited for individuals with severe manifestations. Concurrently, a study from Indus Hospital, Karachi, did not discern any mortality differences with remdesivir use.[25] In contrast, findings from Lahore indicated its effectiveness, especially in cases with less pronounced symptoms, resulting in reduced mortality.[26] Systematic reviews have highlighted the paucity of robust evidence endorsing remdesivir monotherapy for hospitalized

COVID-19 patients.[20] However, meta-analyses have intimated its potential to curtail mortality and disease progression, especially in oxygen-reliant patients without severe manifestations.[27] Contradictorily, the WHO Solidarity Trial Consortium did not confirm its utility in severe cases.[28]

An emergent narrative from the literature posits early remdesivir administration as a modality to preempt severe disease progression.[29,30] In this context, some scholars advocate for its use even in hospitalized patients, not necessitating oxygen therapy.[31]

4.1. Limitations and recommendations

Certain limitations must be acknowledged. Firstly, being a single-center observational study, the findings might be influenced by institutional practices and local patient demographics, which can limit the generalizability of the results to other settings or populations. Secondly, it is crucial to recognize that variations in standards of care among different studies may contribute to disparate results. The influence of institutional practices and local patient demographics across different settings can affect the generalizability of our findings. Thirdly, our sample size was not pre-calculated, which poses a risk of the study being underpowered. An underpowered study can fail to detect a true effect, leading to potential Type II errors. Fourthly, as an observational study, the assignment of patients to the remdesivir or non-remdesivir groups was not randomized. This could introduce confounding variables that might influence the outcomes. Fifthly, the criteria for determining which patients received remdesivir were not detailed, which may introduce selection bias and further impact the validity of the findings. Lastly, without a standardized protocol for treatment and assessment across multiple centers, there might be more variability in the data collected, potentially affecting the results.

It is imperative to put protocols in place that ensure racial and ethnic inclusivity during clinical trials, especially during pandemics and epidemics. This inclusivity will help in capturing the holistic effectiveness and safety profile of the treatment across diverse populations. Future research should involve a power analysis to determine an appropriate sample size. This would reduce the risk of Type II errors and provide a clearer picture of the treatment's effects. Implementing standardized treatment and assessment protocols can reduce variability in data and results. It would be beneficial for the findings to be more consistent and reproducible. Given the varying responses based on disease severity, further stratified analysis or subgroup analysis can help identify specific populations that might benefit most from remdesivir or other treatments. Based on the findings suggesting early intervention benefits, studies focusing on remdesivir's impact during the early stages of the disease, possibly even before hospitalization, would be valuable. Future research can also explore the synergistic effects of remdesivir when combined with other treatments, enhancing its potential therapeutic impact.

5. Conclusion

The therapeutic potential of remdesivir in the context of COVID-19 was evaluated in this study. Our data highlighted a significant association between remdesivir administration and improved survival outcomes, especially among patients with moderate disease severity. This observation corroborates the specific enhancements noted in parameters like SpO 2, ferritin levels, and chest X-ray findings for this subgroup. However, the limited efficacy of remdesivir in patients presenting with severe symptoms highlights the importance of disease stage as a determinant of therapeutic success. Further research is warranted to elucidate the mechanistic underpinnings and optimal therapeutic windows for remdesivir in varied patient cohorts. This study augments the growing body of global COVID-19 literature by providing insights from a Pakistani cohort, further emphasizing the need for regional data to refine treatment protocols tailored to diverse populations. Given the heterogeneous nature of the pandemic's impact, region-specific research remains paramount in guiding global health responses.

Ethical approval

The study received ethical clearance from the Institutional Review Board of King Edward Medical University, as confirmed by the approval letter No: 928/RC/KEMU, dated: 9-12-2020.

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Authors' contributions

All authors played a significant role in the conception, design, data acquisition, analysis, and manuscript review, and gave final approval for publication.

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None.

Conflicts of interest

The authors declare no conflicts of interest in relation to this study.

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