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Original Research Article

Determinant Factors of Clinical Outcome of Remdesivir for The Treatment of SARS-CoV-2 in Indonesia

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ABSTRACT

Remdesivir is an antiviral approved for treating SARS-CoV-2 patients with moderate to severe symptoms. Remdesivir was effective in shortening the recovery time and preventing the severity of SARS-CoV-2 symptoms. This study aims to evaluate the clinical outcomes, side effects, and determinants that influence the clinical outcomes of remdesivir in treating patients with moderate to severe symptoms in Indonesia. An observational study with a cross-sectional design was conducted at a private hospital in East Java from October to December 2024. Retrospective data were collected through patient medical records and pharmacy reports. The WHO SARS-COV-2 seven-point ordinal clinical progression and recovery scale was used to measure patient clinical outcomes. Multivariate logistic regression analysis was performed to predict determinants of clinical outcomes. Ninety-one patients treated with remdesivir from January 2021 to December 2022 were included. This study found that the clinical outcome of patients who recovered or survived after remdesivir treatment was 52% (n=47). There was no significant improvement in clinical progression on days 1 and 6 among surviving patients (p=0.097). Tachycardia was the most common adverse event (n=58), followed by nausea (n=21) and bradycardia (n=18). Length of hospitalization (p=0.009), progression scale on day 1 of admission (p=0.001), and multivitamin medication (p=0.066) were all associated with patient clinical outcomes. The findings of this study highlight that remdesivir effectively prevents worse clinical progression. Longitudinal studies of post-remdesivir treatment in different locations are warranted.

Keywords: Remdesivir, Infectious Disease, Coronavirus, Adverse Event

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has prompted global attempts to develop effective antiviral medicines. Antivirals and other supportive treatments, such as multivitamins and nonsteroidal anti-inflammatory drugs, are required to alleviate SARS-CoV-2 symptoms.[1-4] Remdesivir is an antiviral drug widely used in treating SARS-CoV-2, including in Indonesia. It was initially developed to treat Ebola virus infections and acts as a nucleoside analogue, and inhibits RNA-dependent RNA polymerase (RdRp), an enzyme essential for replicating RNA viruses such as SARS-CoV-2.[5,6] Globally, research on the effectiveness and safety of remdesivir shows mixed results. Several meta-analyses show that remdesivir can reduce mortality in severe SARS-CoV-2 patients and speed up clinical recovery.[7] Several studies have evaluated the effectiveness of remdesivir in accelerating the recovery of SARS-CoV-2 patients.

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Meta-analysis studies show that using remdesivir increases the clinical recovery rate by 21% on day 7 and 29% on day 14. Additionally, remdesivir reduced the need for high-flow oxygen and invasive mechanical ventilation by 27% and 47%, respectively. However, its benefit in reducing mortality remains debated, with results varying across patient populations.[8,9]

The World Health Organization (WHO) has updated its guidelines and recommends using remdesivir for hospitalized and non-hospitalized SARS-CoV-2 patients based on recent data showing reduced mortality or progression to mechanical ventilation in patients not on ventilators.[10,11] Remdesivir can speed up clinical recovery, especially in patients with moderate to severe symptoms.[12] The results of research in America revealed that Remdesivir improved patients' quality of life.[13]

Since the pandemic began, Remdesivir has been used in Indonesia to treat SARS-CoV-2 patients. The findings of a multicenter study evaluating remdesivir efficacy and safety in Indonesia revealed that remdesivir is efficacious and safe in treating SARS-CoV-2 in Indonesia, with an acceptable side effect profile.[14] However, information on factors influencing the clinical outcome of remdesivir is currently scarce. International studies can be helpful, but genetic differences, comorbidities, and regional healthcare systems must all be considered. This study aims to evaluate factors influencing the clinical outcome of remdesivir, especially in the Indonesian context.

Materials and Methods

Study Design
A quantitative observational study with a cross-sectional design. A total sampling involved 91 patients with SARS-CoV-2 who had received remdesivir treatment from January 2021 to December 2022 and met the inclusion criteria.

Ethical Approval
This study was approved by the Ethical Committee Medical Research of Universitas Muhammadiyah Lamongan (Approval Number: 305/EC/KEPK-S3/10/2024). The confidentiality of all participants' data was strictly maintained throughout the research process.

Sample and study location
The study sample included patients with SARS-CoV-2 remdesivir treatment from January 2021 to December 2022 who met inclusion criteria. The study was conducted in a Private Hospital in Lamongan, East Java, from October to December 2024. Eligible subjects were patients diagnosed with moderate to severe symptoms of SARS-CoV-2 who were at least 18 years old and received at least one dose of remdesivir treatment. Patients who had incomplete medical records and died within 48 hours of treatment were excluded.

Instrumentation or Tools
The WHO SARS-CoV-2 clinical progression and recovery scale is a seven-point ordinal scale used to measure patient clinical outcomes. The seven-point ordinal scale was: (1) Patient discharged or outpatient; (2) Patient hospitalized without oxygen support or other treatment; (3) Patient hospitalized without oxygen support but still receiving other treatment; (4) Patient hospitalized using low-flow oxygen support; (5) Patient hospitalized using high-flow oxygen support or non-invasive ventilator; (6) Patient hospitalized using invasive ventilator support or extracorporeal membrane oxygen (ECMO); (7) Death. Clinical improvement was defined as the two-point reduction in the patient's admission status (day 1) to the patient's clinical status on day 6 or live discharge from the Hospital.[15,16]

Data Collection Procedures
The research team gained official permission and confirmation from the research site to collect data. The data sources come from medical records and pharmacy stock reports. The first step was selecting patients with SARS-CoV-2 diagnosed with remdesivir treatment from January 2021 to December 2022 who met the criteria. Furthermore, data on eligible patients were collected. Clinical outcome measures were clinical progression and recovery, D-dimer elevation, and adverse drug events during remdesivir treatment.

Data Analysis
The Statistical Package for Social Science (SPSS) by IBM, version 26.0 for Windows, was utilized for data analysis. Descriptive analyses were conducted to present patient and medication characteristics, clinical status progression, adverse drug event profiles, and D-dimer profiles. The Wilcoxon signed-rank test was performed to find the difference analysis between clinical outcome progression recovery on day 1 and day 6 and D-dimer value before and after remdesivir treatment. The predictors of remdesivir clinical outcomes for treating SARS-CoV-2 were determined using multivariate logistic regression analysis. Estimate the strength of the association using an adjusted odds ratio (AOR) with a 95% confidence interval. The refinement of the final model is conducted using a step-by-step elimination method, which involves sequentially removing variables with a p-value of 0.25 or higher. The final model includes variables with a p-value of less than 0.05, as well as those that significantly impact the dependent variables.

Results and Discussion

Data from 1,414 medical records of patients diagnosed with SARS-CoV-2 between January 2021 and December 2022 were reviewed. Of these, 105 patients received remdesivir treatment during the same period, with 91 of those patients meeting the eligibility criteria for the study. Table 1 describes patient and medication characteristics. The range age between 45 and 60 was dominant; 53% of the patients were female, and the average Length of Stay (LoS) was 7 days. The most common comorbidity was diabetes, followed by hypertension and cardiovascular diseases. The most frequently used antibiotics were macrolides (35.16%), cephalosporin (22%), fluoroquinolones (14.29%), and meropenem (7.69%). Dexamethasone (67.03%) and Heparin (48.35%) were the most frequently used corticosteroids and anticoagulants.
a: one patient can have more than one comorbid; b: one patient may receive more than a single antibiotic; c: one patient may receive more than a single anticoagulant

Clinical Outcome
In this observational study, the mortality of SARS-CoV-2 patients with remdesivir treatment was 48%. Clinical outcome with patients recovering or alive after remdesivir treatment was 52% (see Figure 1). Patient condition factors, including symptom severity, age, gender, secondary bacterial infection, and comorbidities, were associated with a high mortality rate.[17,18] Furthermore, the WHO SARS-CoV-2 Progression and Recovery Scale was used to assess live patients. Table 2 shows that most patients were in category 4 of the seven-point ordinal scale of clinical status on day 1. Then, the Wilcoxon signed-rank test was performed. The results showed that 30 patients had not experienced changes in clinical outcomes, 11 had experienced improvement, and six had experienced worsening conditions. Unfortunately, there was no significant clinical progression improvement on day-1 and day-6 treatment (p=0.097).

Table 1: Patient and Medication Characteristics

No	Characteristic	Frequency	%
1	Gender		
	Male	43	47
	Female	48	53
2	Age (year)		
	25-35	16	17.58
	36-45	13	14.29
	45-60	33	36.26
	>60	29	31.87

3	Length of Stay (day)		
	≤6	57	62.64
	7-15	29	31.87
	16-25	4	4.4
	>25	1	1.1
6	Comorbidities[a]		
	Diabetes Mellitus	24	26.37
	Hypertension	14	15.38
	Cardiovascular	12	13.19
	None	49	53.85
7	Antibiotics[b]		
	Macrolides	32	35.16
	Fluoroquinolones	13	14.29
	Cephalosporin	20	22
	Meropenem	7	7.69
	None	26	28.57
8	Corticosteroids		
	Dexamethasone	61	67.03
	Methylprednisolone	1	1.1
	None	29	31.87
9	Anticoagulants[c]		
	Heparin	44	48.35
	Enoxaparin	7	7.69
	Fondaparinux	23	25.27
	None	29	31.87

Table 2: Patient Clinical Status Based on WHO SARS-CoV-2 Progression and Recovery Scale

Clinical Status	**Scale**	**Day-1 N (%)**	**Day-6 N (%)**	***P* Value**
Patient discharged or outpatient	1		5 (10.64)	0.097
Patient hospitalized without oxygen support or other treatment	2	18 (38.30)	18 (38.30)	
The patient was hospitalized without oxygen support but still receiving other treatment	3	1 (12.13)	1 (12.13)	
The patient was hospitalized using low-flow oxygen support	4	26 (55.32)	19 (40.43)	
Patient hospitalized using high-flow oxygen support or non-invasive ventilator	5	5 (4.25)	4 (8.50)	
Patient hospitalized using invasive ventilator support or extracorporeal membrane oxygen (ECMO)	6	0 (0.00)	0 (0.00)	

Nevertheless, remdesivir treatment was proven to maintain the stability of the patient's condition.[15,16,19,20] The finding of this study is consistent with previous studies that indicate remdesivir clinical outcome progression did not significantly improve in the first week of treatment. Clinical progression improvement was in line with the length of stay.[16,21] Hence, the guideline adapted the duration of remdesivir treatment for SARS-CoV-2 patients within 10 days of illness.[22]

However, our findings contrast Hadiatussalamah et al. (2023) and Garibaldi et al. (2021), who reported significant improvement in clinical outcome progression in the first week.[15,23] Nevertheless, remdesivir treatment has prevented worse patient clinical conditions and decreased mortality rates significantly in elderly patients treated and not treated with remdesivir.[21,24]

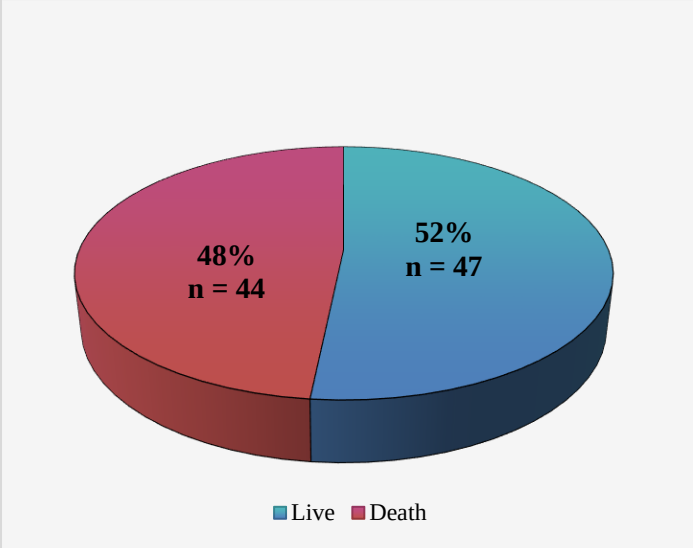

Figure 1: Clinical Outcome of SARS-CoV-2 Patient with Remdesivir Treatment

Adverse Drug Events

Adverse events recorded on the patient's medical record were tachycardia, nausea, bradycardia, and vomiting (see Figure 2). Every patient might experience more than one side effect. Adverse events, including nausea, vomiting, tachycardia, and bradycardia, were recorded in grade mild to moderate side effects.[25] The recorded adverse events may also be due to other causes, such as the patient's condition and medications with similar side effects. Cardiac adverse events such as tachycardia and bradycardia were the most common in hospitalized patients with SARS-CoV-2 who received remdesivir. This finding aligns with Terzić et al. (2024) and Poliseno et al (2021), who reported that bradycardia and tachycardia were the most common adverse effects recorded after remdesivir administration.[26,20] Besides, our findings are opposite of those of Ghahremanian et al. (2023), who reported that hepatic dysfunction was the most prevalent adverse event among remdesivir recipients.[27] The side effects of tachycardia and bradycardia, particularly, were influenced by the adenosine analogue properties of remdesivir. On the other hand, the potential role of remdesivir in the occurrence of cardiac events and the mechanism of bradycardia induction are not yet clear, notably due to the complex confounding factors such as SARS-CoV-2 disease itself and other concomitant medications that can induce cardiac adverse manifestations.[28]

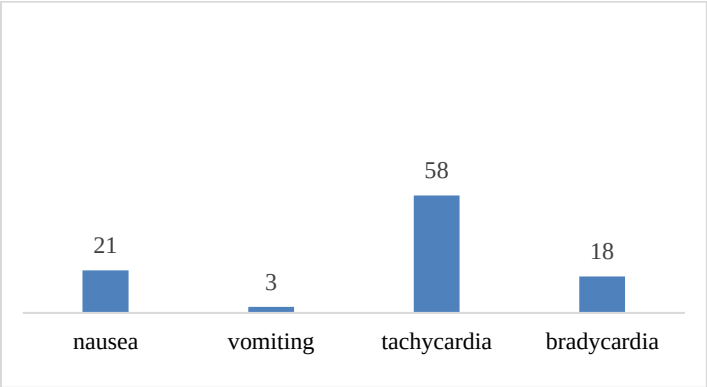

Figure 2: Adverse Drug Event

Table 3 shows that the median D-dimer value before treatment was 0.815 and 1.985 after treatment. Our findings revealed a significant (p= 0.004) D-dimer elevation before and after remdesivir treatment.[29] D-dimer levels are parameters used in clinical practice as sensitive biomarkers in evaluating venous thromboembolism.[30] Increasing D-dimer level, post remdesivir treatment in this study, was similar to several studies showing that increased D-dimer levels in SARS-CoV-2 patients were associated with higher mortality.[31-34] Anticoagulant agents were administrated to minimize D-dimer elevation during remdesivir treatment. Our findings showed that anticoagulant agent treatment was inappropriate or had no significant decrease in D-dimer levels in SARS-CoV-2 patients with severe symptoms.[35] Nevertheless, anticoagulant treatment has significantly decreased D-dimer values in SARS-CoV-2 patients with mild to moderate symptoms.[36]

Table 3: Patient D-dimer Profile Pre and Post Remdesivir Treatment

D-dimer	Minimum (µg/ml)	Maximum (µg/ml)	Median (µg/ml)	Interquartile range (µg/ml)	*P* Value
Pre	0.19	56.36	0.815	1.0475	0.004
Post	0.10	42.50	1.985	5.265	

Determinant Factors of Clinical Outcome

This study evaluated the determinant factors of the clinical outcome of patients receiving remdesivir treatment. Based on the study's results, several factors significantly affect clinical outcomes, although some other factors do not show a considerable impact. Table 4 shows the analysis of determinants of clinical outcomes for patients treated with remdesivir. In this study, there were two groups of patients: survivors (47 patients) and those who died (44 patients). Based on Table 4, the gender variable did not show a significant association with clinical outcomes. Male and female patients had a relatively comparable chance of achieving recovery or death (95% CI = 0.266 to 1.398, p = 0.242), indicating that gender did not play a significant role in determining the clinical outcome of this treatment. In addition, the age factor was also not proven to have a substantial effect. Patients over 60 years of age, although they tended to have higher survival rates, did not show a significant difference compared to patients aged 60 years and younger (95% CI = 0.218 to 1.322, p = 0.176). Meanwhile, although the presence of comorbidities such as hypertension, diabetes, or other conditions is often a concern in the treatment of patients, this study found no significant evidence that comorbidities affected clinical outcomes in patients receiving remdesivir treatment (95% CI = 0.347 to 1.812, p = 0.582). Research by Beigel et al. on remdesivir also shows that although comorbidities can worsen a patient's condition, this antiviral therapy still benefits most patients regardless of their comorbid status.[3]

In addition, the use of antibiotics did not show significant differences in the clinical development of patients. Patients who took antibiotics and anticoagulants did not have statistically different outcomes compared to those who did not use the therapy, with high p-values (95% CI = 0.355-2.199, p = 0.791). Although antibiotics are often used to treat secondary infections that may arise during viral infections, the use of antibiotics does not always directly impact the success of remdesivir treatment. Previous research has shown that routine use of antibiotics in managing SARS-CoV-2 without evidence of active bacterial infection can increase the risk of side effects and affect the patient's body microbiota, ultimately not improving clinical outcomes.[37] In addition, studies by Evans et al. also emphasized that improper use of antibiotics in SARS-CoV-2 patients can worsen the patient's condition, lead to antibiotic resistance, and increase the duration of treatment.[38]

Anticoagulants did not show a significant association with clinical outcome in this study (95% CI = 0.504 to 2.948, p = 0.660) due to the complexity of managing patients with SARS-CoV-2 who require anticoagulants, which are often used to manage the increased risk of thromboembolism in patients with viral infections. Nonetheless, some studies suggest that anticoagulants can improve the prognosis of patients with COVID-19 by preventing blood clotting complications, especially in patients with severe conditions. A meta-analysis by Jiang L et al. suggests that using anticoagulants in SARS-CoV-2 patients may reduce mortality, although this use must be adapted to the patient's clinical condition.[39] Research by Thachil et al. also supports these findings, showing that while not all SARS-CoV-2 patients require anticoagulants, more severe patients at high risk of thrombosis benefit from anticoagulant therapy.[40]

Length of stay hospitalized.

In contrast, the results of multivariate analysis indicate that length of stay of hospitalized, scale progressivity on day 1, and multivitamin treatment significantly influenced patient's clinical outcome with remdesivir treatment (see Table 4). The variable length of hospitalization showed a significant influence on the clinical outcome of patients. Patients hospitalized for more than 7 days had a much greater chance of survival than those hospitalized for less than 7 days (95% CI = 0.071 to 0.691, p = 0.009). The average length of stay for patients receiving remdesivir is about 7.5 days, with some cases up to 88 days.[41] This duration can be affected by the timing of remdesivir, as early treatment can lead to a faster recovery. Early administration of remdesivir, especially in the first few days of symptom onset, has been associated with improved clinical outcomes, including reduced need for high-flow oxygen therapy and ICU admission. Early administration of remdesivir (within 0-3 days of symptom onset) has a lower likelihood of requiring high-flow oxygen therapy and ICU admission compared to subsequent administration (≥4 days).[42] In addition, patients who received remdesivir within three days had a much lower risk of developing severe disease than those treated later.[43]

Patient severity

The severity of the patient's condition on first day treatment based on the WHO SARS-CoV-2 Progression and Recovery Scale significantly influenced the clinical outcome of remdesivir treatment (see Table 4). This study found that patient's admission with scale progressivity on day-1 categories scale 4 (The patient was hospitalized using low-flow oxygen support) and scale 5 (Patient hospitalized using high-flow oxygen support or non-invasive ventilator) significantly influenced the clinical outcome and had a high-risk of death (p = 0.003; p = 0.001). A meta-analysis found no significant decrease in 28-day all-cause mortality among ventilated patients, although unventilated patients showed lower hospital mortality rates.[44] Another study showed that remdesivir was more effective in patients with moderate SARS-CoV-2. One study found that moderately ill patients had a much lower mortality rate (5.9%) compared to critically ill patients (34.8%) when treated with remdesivir.[45]

Multivitamins treatment

This study found that patients who received multivitamins treatment had a lower mortality rate, as multivitamins enhance immunity and support healing (95% CI = 0.868 to 74.787, p = 0.066). While multivitamins do not replace primary treatment, an improved nutritional status can enhance patient outcomes. Some studies have not directly addressed the complex relationship between taking multivitamins and the incidence of death in patients receiving remdesivir treatment for SARS-CoV-2. Multivitamins, in general, have not shown significant protective effects on mortality in various health conditions, including cardiovascular disease.[46] In the context of SARS-CoV-2, specific vitamins such as vitamin D have been studied more extensively, with some evidence suggesting potential benefits in reducing mortality, although the results are mixed and inconclusive.[47-4]

Remdesivir, on the other hand, has been associated with a decrease in mortality in specific subgroups of SARS-CoV-2 patients, especially those who do not require high-flow oxygen or mechanical ventilation.[50] Some studies have shown an inverse relationship between vitamin D levels and SARS-CoV-2-related deaths, suggesting that higher vitamin D levels may be associated with lower mortality rates.[48] However, the meta-analysis found no significant mortality benefit from vitamin D supplementation in SARS-CoV-2 patients.[51] Studies have examined the effects of Vitamin C and B complexes, but the evidence regarding their effectiveness in reducing SARS-CoV-2 mortality remains limited and not statistically significant.[49] Although multivitamins have not been shown to significantly reduce mortality, specific vitamins, such as vitamin D, may offer some protective effects against SARS-CoV-2-related mortality. Remdesivir, on the other hand, has demonstrated a mortality benefit in specific patient groups, indicating that its use may be more effective than multivitamin supplementation in lowering mortality rates among SARS-CoV-2 patients. However, studies have not explicitly examined the direct interaction between multivitamin use and remdesivir treatment and mortality outcomes. Thus, the results of this study emphasize the importance of factors such as length of hospitalization, scale of disease severity, and the use of multivitamins in managing and treating patients with SARS-CoV-2.

Study Limitations

Although this study has milestone contributions in providing pharmacovigilance data for remdesivir treatment and improving preparedness to overcome similar disasters, several limitations should be acknowledged. The cross-sectional retrospective study design is restricted to establishing causality, which aligns with the constraints identified by earlier studies.[52] In addition, this study was conducted in only one location. Therefore, longitudinal studies with multiple sites to address these limitations and provide more in-depth insights. Future research could consider long-term effects post remdesivir treatment, and expanding studies, including numerous sites with large sample sizes, could also contribute to the global impact.

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Table 4: Determinant Factors of Clinical Outcome Patient with Remdesivir Treatment

Characteristics	Clinical Progression				Bivariate analysis			Multivariate analysis		
	Alive (n=47)		Dead (n=44)		Crude Odds Ratio (COR)	95% CI	P-value	Adjusted Odds Ratio* (AOR)	95% CI	P-value
	n	%	n	%						
Gender										
Female	22	45.83	26	54.17	1.00	Reference				
Male	25	58.14	18	41.86	0.609	0.266-1.398	0.242			
Age (year)										
≤60	29	46.77	33	53.23	1.00	Reference				
>60	18	62.07	11	37.93	0.537	0.218-1.322	0.176			
Length of stay (day)										
<7	21	36.84	36	63.16	1.00	Reference		1.00	Reference	
≥7	26	76.47	8	23.53	0.179	0.069-0.468	0.000	0.221	0.071-0.691	0.009
Comorbid										
No	24	49	25	51	1.00	Reference				
Yes	23	54.76	19	45.24	0.793	0.347-1.812	0.582			
Antibiotic										
Yes	33	50.77	32	49.23	1.00	Reference				
No	14	53.85	12	46.15	0.884	0.355-2.199	0.791			
Corticosteroid										
Yes	28	45.16	34	54.84	1.00	Reference				
No	19	65.52	10	34.48	0.433	0.174- 1.082	0.073			
Anticoagulant										
Yes	33	53.23	29	46.77	1.00	Reference				
No	14	48.28	15	51.72	1.219	0.504-2.948	0.660			
Multivitamin										
Yes	43	59.72	29	40.27	1.00	Reference			Reference	
No	4	21.05	15	78.95	5.560	1.676-18.448	0.005	8.056	0.868-74.787	0.066
Scale of progressivity on day I										
Scale 2	18	94.74	1	5.26	1.00	Reference			Reference	
Scale 3	1	100	0	0	0.00	0.00	1.00	0.000	0.000	1.000

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Scale 4	26	44.07	33	55.93	22.846	2.859 – 182.547	0.003	48.691	3.727 – 636.041	0.003
Scale 5	2	16.67	10	83.33	90.000	7.228 – 1120.650	0.000	158.331	7.815 – 3207.797	0.001
Category D-dimer on day I										
Normal	17	77.27	5	22.73	1.00	Reference				
High	29	43.28	38	56.72	4.455	1.471-13.492	0.008			

*Adjusted each other between the variables listed in this table

Conclusion

In summary, this study's findings demonstrated that remdesivir treatment has prevented worse patient clinical conditions and decreased mortality rates. Length of stay, scale progression of the disease, and multivitamin treatment affected the patient's clinical outcome. While this study provides valuable insights into providing a pharmacovigilance database and improving preparedness to overcome similar disasters, limitations should be noted, such as lack of sample size and single site study. Future research should focus on long-term effects post remdesivir treatment and expanding studies, including various sites with larger sample sizes.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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