Original Article

Remdesivir in COVID-19: A Retrospective Analysis of Remdesivir Effectiveness and the Relation with Blood Type Variation

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Abstract

Background: Remdesivir has been proven effective for COVID-19 treatment. This research aims to identify the profile of the effectiveness of Remdesivir (RDV) therapy and its relationship to blood type variations in COVID-19 patients at Universitas Indonesia Hospital (RSUI).

Methods: Variations in blood types were examined for their influence on the effectiveness in COVID-19 infected patients with RDV as an antiviral treatment. Data for this study were acquired at RSUI using a retrospective cross-sectional method. The sample is infected patients with COVID-19 from January 2021 to December 2021 who received RDV therapy. The parameters of the effectiveness of the treatment was a reduction of minimally 2 points on the WHO Clinical Progression Scale after 14 days of Remdesivir administration.

Results: RDV effectiveness percentage shows 57.5% of patients experienced clinical improvement. The analysis results of the effect of blood type variations on clinical outcomes significantly affect the effectiveness of RDV therapy (OR=1.705; 95% CI=1.091–2.665; *P*=0.019) but insignificant in terms of mortality status (OR=0.654; 95% CI=0.383–1.117; *P*=0.120).

Conclusion: Blood type variations significantly affected the effectiveness of RDV therapy in infected COVID-19 patients.

Keywords: antiviral, blood type variations, COVID-19, clinical outcome, remdesivir

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INTRODUCTION

The new viral disease, COVID-19, was first discovered in 2019, specifically in Wuhan, China. From there, it expanded to nearly all the nations around the world.[1] On March 2nd, 2019, two patients from Jakarta were accused in the nation's first COVID-19 infection case in Indonesia. Then, the total number of patients confirmed positive for COVID-19 was 38,277, with 2,134 deaths on June 15, 2020. The number of patients infected by COVID-19 and the number of death increases every day.[2]

Direct and indirect contact are methods by that SARS-CoV-2 can be spread. Direct contact refers to person-to-person and droplet transmission, and indirect contact refers to contaminated objects and airborne transmission. A source of airborne transmission can also be spread from PPE (personal protective equipment).[3]

Pharmacological therapy in patients infected by COVID-19 is categorized based on the degree of severity. The severity of COVID-19 patients is grouped into severe to critical symptoms, moderate, mild, and asymptomatic. Difference symptoms need a different treatment.[4]

The FDA, commonly known as Food and Drug Administration, recently approved intravenous RDV as an antiviral treatment for adults and children with COVID-19 (aged 12 years and weight 40 kg). It is approved for the antiviral therapy of non-hospitalized COVID-19 patients (i.e., on day 3 with 7 days following the onset of symptoms), inpatients (i.e., on day 5), and antiviral therapy for mild symptoms to moderate symptoms in high-risk of COVID-19.[4] RDV is used for COVID-19 patients with moderate and severe symptoms in Indonesia.[5]

RDV (GS-5734) is the first FDA-approved therapy for severe COVID-19. RDV (GS-5734) is an analog of adenosine nucleotide that is active against a broad spectrum of single-stranded RNA viruses, including emerging and zoonotic coronaviruses such

as 2019-nCoV3, MERS-CoV, and SARS-CoV. The drug was first described in 2016 and was derived from a small molecule antiviral library to target emerging pathogenic RNA viruses. RDV is a monophosphoramidate whose action is blocking RNA production and inhibiting RNA polymerase proofreading.[6]

Referring to previous research, RDV is a pretty effective antiviral for COVID-19 treatment. Research conducted by Gupte in India shows that RDV administration can increase 84% of clinical improvement, while research by Olender reveals that the percentage of clinical improvement reaches 74.4% with RDV administration on day 14 compared to without RDV administration.[7,8]

Research on blood type variations concerning the severity, mortality rate, and risk of COVID-19 infection has been widely conducted. Patients with the O blood have the lowest risk of infection but have milder symptoms than other blood type variations.[9] Meanwhile, AB patients are a risk factor for high mortality.[10]

There has not been any significant research examining the variation of blood types and the effect on RDV antiviral effectiveness. However, the study conducted by Du et al examines the effect of blood type variations on propofol effectiveness and reveals that blood type variations affect the effectiveness of propofol.[11]

METHODS

This observational study used a cross-sectional design. Data sources were medical record data of COVID-19 inpatients at RSUI. Data were collected retrospectively using specified inclusion and exclusion criteria. The sample of this research was COVID-19 inpatients receiving RDV therapy in 2021.

The data to be collected includes blood type, patient demographics, and clinical outcomes. The effectiveness of the treatment was measured by WHO Clinical Progression Scale consisting of 5 levels of the patient's clinical condition with a score range of 0 (uninfected) – 10 (died). After analyzing the WHO Clinical Progression Scale, the effectiveness of therapy was analyzed for its relationship with the blood type variation. Data analysis covered descriptive analysis and inferential statistics using Chi-square.[1]

The University of Indonesia Hospital Ethics Committee approved the research protocol under number S-026/KETLIT/RSUI/VII/2022. Since there is no direct interaction with the patient, the Ethics Committee omitted the requirement for consent.

RESULTS

From January to December 2021, 295 out of 1542 confirmed Covid-19 patients were treated with RDV therapy. Then, 80 of 259 patients were randomly selected according to the inclusion and exclusion criteria.

Table 1. Patient Demographics

Category	N (%)
Gender	
Male	51 (63.8%)
Female	29 (36.3%)
Blood type	
A	22 (27.5%)
AB	10 (12.5%)
B	15 (18.8%)
O	33 (41.3%)
Age, year (Mean±SD)	56.74±11.339
18-59	47 (58.8%)
≥60	33 (41.3%)
Oxygen therapy	
Yes	73 (91.3%)
No	7 (8.8%)
Number of comorbid	
0	4 (5.0%)
1	15 (18.8%)
>1	61 (76.3%)
History of comorbid	
No	4 (5.0%)
Yes	76 (95.0%)
Comorbid	
HT	47 (58.8%)
DM	44 (55.0%)
Respiratory disorders	5 (6.3%)
Immunity disorders	0 (0.0%)
Kidney disorders	21 (26.3%)
Obesity	12 (15.0%)
CVD	27 (33.8%)
HT+DM	23 (28.8%)
HT+CVD	13 (16.3%)
DM+CVD	13 (16.3%)
HT+DM+CVD	12 (15.0%)

Note: HT=Hypertension; DM=Diabetes Mellitus; CVD=Cardiovascular Disease

This research involved 80 COVID-19 patients who received RDV therapy. Based on gender, the

patients comprised 63.80% male and 36.30% female. The most common blood type is type O, with a percentage of 41.3%. The patients are dominated by patients aged 18-59 years (58.8%) and followed by those aged ≥ 60 years (Table 1).A total of 73 patients out of 80 patients received oxygen therapy with a percentage of 12.33% using intubation and ventilators. The results showed that 95.0% of patients had comorbidities, and 61 had more than one comorbid. The most common comorbid was HT (hypertension) (58.8%) then, followed by diabetes (55.0%), cardiovascular (33.8%), kidney disorders (26.3%), obesity (15.0%), and respiratory disorder (6.3%). The most common comorbid combinations were hypertension-diabetes, with an incidence of 28.2%, followed by hypertension-cardiovascular and diabetes-cardiovascular, with a percentage incidence of 16.3% each. The comorbid combination of hypertension, diabetes, and cardiovascular reached 15.0%.

The patients were given 200mg of RDV intravenously as the initial dose on the first day, followed by 100mg of RDV as a maintenance dose for the next four days. After 14 days of RDV therapy, the clinical improvement was checked based on the point decrease of the WHO Clinical Progression Scale score by minimally 2 points. Based on the clinical status of the patients, 46 patients (57.5%) of 80 patients experienced clinical improvement, and nine patients experienced a decrease of 1 score. A total of 14 patients (17.5%) died after the administration of RDV antiviral therapy, and one died before RDV therapy.

According to the graph (Figure 1), the variation in the percentage of blood types A and O in enhancing clinical outcomes and lowering deaths in COVID-19 patients receiving RDV antiviral medication was more significant than in individuals with blood types B and AB. The percentage, OR, and value of *P* of each blood type variation can be seen in the table of bivariate analysis results in Tables 4 and 5.

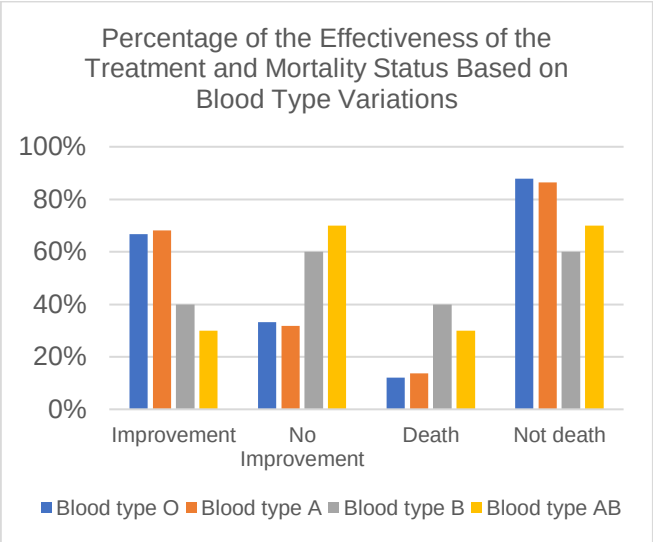

Figure 1. Percentage of the Effectiveness of the Treatment and Patient Mortality Status Based on Blood Type Variations

Table 2. General Characteristics of Patients Based on Blood Type Variations

Characteristics	Blood type				*P*
	A n (%)	B n (%)	AB n (%)	O n (%)	
Clinical outcome					
Improvement	15 (68.2%)	6 (40.0%)	3 (30.0%)	22 (66.7%)	0.068
No improvement	7 (31.8%)	9 (60.0%)	7 (70.0%)	11 (33.3%)	0.068
Death status					
Yes	3 (13.6%)	4 (26.7%)	3 (30.0%)	4 (12.1%)	0.416
No	19 (86.4%)	11 (73.3%)	7 (70.0%)	29 (87.9%)	0.416
Gender					
Male	16 (72.7%)	10 (66.7%)	4 (40.0%)	21 (63.6%)	0.353
Female	6 (27.3%)	5 (33.3%)	6 (60.0%)	12 (36.6%)	0.353
Number of comorbidities					
No comorbid	1 (4.5%)	1 (6.7%)	0 (0.0%)	2 (6.1%)	0.873
1 comorbid	4 (18.2%)	2 (13.3%)	1 (10.0%)	8 (24.2%)	0.873
>1 comorbid	17 (77.3%)	12 (80.0%)	9 (90.0%)	23 (69.7%)	0.873
Age (Mean±SD)	55.64±13.106	59.20±6.527	61.50±9.880	54.91±12.017	
Adult	12 (54.5%)	9 (60.0%)	5 (50.0%)	21 (63.6%)	0.847
Elderly	10 (45.5%)	6 (40.0%)	5 (50.0%)	12 (36.4%)	0.847

Note: SD=Standard Deviation

Table 3. Multivariate Analysis of the Effectiveness of RDV Antiviral Therapy

	Risk Factor	WHO Clinical Progression			Mortality Status		
		OR	95% CI	*P*	OR	95% CI	*P*
Crude	Blood Type.	1.705	1.091–2.665	0.019	0.654	0.383–1.117	0.12
Adjusted	Blood Type	1.32	0.751–2.319	0.334	0.832	0.398–1.738	0.625
	Gender	1.01	0.308–3.318	0.987	1.669	0.288–9.678	0.568
	Age, years	1.882	0.585–6.058	0.289	3.396	0.511–22.569	0.206
	Comorbid	0.486	0.066–3.572	0.478	2.779	0.228–33.890	0.423
	Hypertension	0.022	0.000–1.105	0.056	2.446	0.071–84.123	0.62
	Diabetes mellitus	0.012	0.000–0.676	0.032	0.719	0.018–28.522	0.86
	Respiratory disease	0.12	0.006–2.523	0.172	17.633	0.779–398.931	0.071
	CVD	0.005	0.000–0.443	0.02	39.226	0.607–2534.764	0.084
	Kidney diseases	0.311	0.072–1.346	0.118	3.77	0.692–20.552	0.125
	Obesity	0.203	0.024–1.723	0.144	17.513	1.502–204.196	0.022
	HT+DM	1.324	0.267–201.031	0.239	31.174	0.755–1286.656	0.07
	HT+CVD	57.57	2.078–1595.103	0.017	0.068	0.001–5.797	0.236
	DM+CVD	52.342	1.537–1781.904	0.028	0.741	0.012–44.149	0.236
	HT+DM+CVD	0.315	0.051–1.940	0.213	0.291	0.006–13.329	0.527

Note: HT=Hypertension; DM=Diabetes Mellitus; CVD=Cardiovascular Disease; CI=Confidence Interval; OR=Odd Ratio

Based on the statistical data in Table 2, patients infected with COVID-19 with blood type variation A (68.2%) and O (66.7%) have a higher percentage of improvement. Meanwhile, patients with blood type B (40.0%) and AB (30%) have a smaller percentage of improvement. The highest mortality status is found in patients with blood type AB (30.0%), followed by type B (26.7%), A (13.6%), and type O (12.1%).

The logistic regression analysis indicated that blood type variations had a significant effect on the effectiveness of RDV antiviral therapy (OR=1.705; 95% CI=1.091–2.665; *P*=0.019) but did not significantly affect mortality status (OR=0.654; 95% CI=0.383–1.117; *P*=0.120). Meanwhile, when influenced by other confounding variables, blood type variation did not significantly affect the effectiveness of RDV antiviral therapy (OR=1.320; 95% CI=0.751–2.319; *P*=0.334).

Based on the analysis result of the effect of blood type variations on the effectiveness of RDV therapy using the Chi-square test (Table 4), RDV therapy for COVID-19 patients with blood types variations A and O have effectiveness of 1.866 (95% CI=0.633–5.254; *P*=0.313) and 1.917 (95% CI=0.762–4,821; *P*=0.178) times better in improving patient clinical outcomes compared to other blood types.

The percentage of improvement in RDV therapy in COVID-19 patients with blood types A (68.2%) and O (66.7%) is higher than the other blood types (53.4% and 51.1%) with OR of 1.866 and 1.917, respectively. It can be said that blood type A has proven to have 1.866 times the effectiveness of RDV therapy, and blood type O has 1.917 times better in improving patient clinical outcomes compared to other blood types.

The percentage of improvement in COVID-19 patients with RDV antiviral therapy in patients with blood type B (40.0%) and type AB (30.0%) is lower than the other blood types (61.5% and 61.4%). On the other hand, the percentage of no improvement in COVID-19 patients with RDV antiviral therapy with blood type B (60.0%) and type AB (70.0%) is higher than the blood types (38.5% and 33.3%). Based on the Chi-square test results on the effect of blood type variations on the effectiveness of RDV therapy (Table 5), blood type O (OR=0.51; 95% CI=0.145–1.794; *P*=0.376) and blood type A (OR=0.675; 95% CI=0.169–2.691; *P*=0.747) are a protective factor in the possible mortality status.

The percentage of mortality status in blood type A (13.6%) and type O (12.19%) is lower than the other blood types (19.0% and 21.3%). This result indicates that individuals with blood types A and O have a reduced probability of death than those with non-A and non-O. The blood type non-A refers to blood types O, B, and AB, whereas blood types A, B, and AB are referred to as type non-O.

Table 4. Bivariate Analysis of the Effectiveness of RDV Antiviral Therapy based on the WHO Clinical Progression Scale

Blood Type		WHO Clinical Progression		OR	95% CI	*P*
		Improvement	No improvement			
		n (%)	n (%)			
A	Yes	15 (68.2%)	7 (31.8%)	1.866	0.633–5.254	0.313
	No	31 (53.4%)	27 (46.6%)			
B	Yes	6 (40.0%)	9 (60.0%)	0.417	0.132–1.313	0.155
	No	40 (61.5%)	25 (38.5%)			
AB	Yes	3 (30.0%)	7 (70.0%)	0.269	0.064–1.131	0.088
	No	43 (61.4%)	27 (38.6%)			
O	Yes	22 (66.7%)	11 (33.3%)	1.917	0.762–4.821	0.178
	No	24 (51.1%)	34 (48.9%)			

Note: CI=Confidence Interval; OR=Odd Ratio

Table 5. Bivariate Analysis of the Effectiveness of RDV Antiviral Therapy based on the Mortality Status

Blood Type		Mortality status		OR	95% CI	*P*
		Yes	No			
		n (%)	n (%)			
A	Yes	3 (13.6%)	19 (86.4%)	0.675	0.169–2.691	0.747
	No	11 (19.0%)	47 (81.0%)			
B	Yes	4 (26,7%)	11 (73.3%)	2	0.530–7.547	0.286
	No	10 (15.4%)	55 (84.6%)			
AB	Yes	3 (30.0%)	7 (70.0%)	2.299	0.514–10.280	0.368
	No	11 (15.7%)	59 (84.3%)			
O	Yes	4 (12.1%)	29 (87.9%)	0.51	0.145–1.794	0.376
	No	10 (21.3%)	31 (78.7%)			

Note: CI=Confidence Interval; OR=Odd Ratio

Unlike blood types A and O, patients with B and AB seemed to have no reduced probability of death than those with non-B and non-AB. The percentage of death patients in blood type B (26.7%) and type AB (30%) is higher than the other types (13.6%) and (12.1%). In blood types A and O, the mortality status is lower than type non-A and type non-B. This result is proven by the percentage of patients who did not die with blood type A (86.4%) and blood type O (87.9%) higher than the other types (81.0% and 78.7%).

DISCUSSION

Based on the collected data, the percentage of male patients (63.8%) is higher than females (36.3%). Based on Table 2, the general characteristics of patients are based on blood type variations, in general, male patients with different blood types have a higher percentage than female patients (*P*=0.353). This is consistent with previous research by Magdalena et al in a hospital in Malang that men are at a higher of getting infected by COVID-19 (OR=2.202; 95% CI=0.994–4,878; *P*=0.050).[12]

However, there is no difference in the proportion of gender among the COVID-19-infected patients, according to a comprehensive review analysis by Peckham et al that included 97 pieces of evaluated literature. However, compared to female patients, male patients had a higher probability of disease development to the severity and increased mortality risk.[13]

Viral load, oxygen therapy, and patient clinical improvement are essential parameters for the effectiveness of the treatment for COVID-19 patients. All aspects to see the effectiveness of the therapy can be seen in the WHO Clinical Progression Scale.[13] In our study, the analysis of the effectiveness of RDV therapy based on the WHO Clinical Progression Scale shows that 57.5% of COVID-19 patients experience improvement. This percentage is lower than the previous study by Olender et al, where the percentage of effectiveness of the treatment reaches 74.4%.[8]

Patients requiring oxygen therapy via a mechanical ventilator and ECMO were excluded from this study. This is one of the reasons why the effectiveness of RDV therapy is lower than in the previous study by Olender et al. Another study by

Henry B shows that patients using ECMO are predictors of death due to COVID-19.[14]

The examination result of the effect of the variation of blood type on RDV effectiveness shows that blood type variations have a significant effect on the effectiveness of RDV antiviral therapy (OR=1.705; 95% CI=1.091–2.665; *P*=0.019). The effect of variation of blood type on RDV effectiveness has not been specifically researched. However, there is research on the effect of blood type on effectiveness by Du et al in Mongolia. Du et al examine the anesthetic effect of propofol on patients with different blood types. The research reveals that variations in blood type may produce different effects on clinical outcomes.[11]

Examination results of the influence of blood type variations on clinical outcomes while influenced by covariates did not significantly lead to conclusive findings (OR=1.320; 95% CI=0.751–2.319; *P*=0.334). It may be due to the influence of comorbid factors that affect clinical outcomes, severity, and even death. Petrilli et al reveal that age and comorbidities strongly predict hospitalization, critical severity, and death.[15]

Obesity, cerebrovascular diseases, renal illness, respiratory issues, hypertension, CVD, diabetes mellitus, and malignancy are among the comorbidities that increase the likelihood of COVID-19's severity.[16] Gender and age are risk predictors for the severity degree and severity development of COVID-19, according to the comprehensive review study and meta-analysis conducted by Fathi et al Additionally, men who are older and have comorbid conditions are more likely to experience severe COVID-19 symptoms.[17]

In this study, the most significant comorbid in preventing the improvement of the patient's clinical condition is CVD, either single comorbid (*P*=0.02) or in combination with DM (*P*=0.028) and HT (*P*=0.017) and also DM as single comorbid without other combination (*P*=0.032). Meanwhile, obesity is a comorbid factor that elevated the probability of death in COVID-19 patients receiving RDV treatment (*P*=0.022). The patients who previously had comorbid CVD, as showed by Zhang et al are more prone to deterioration. According to Zhang et al, COVID-19 patients suffering from CVD are more likely to have impaired liver function, elevated blood creatinine, and lactate dehydrogenase (*P*<0.05).[18]

This also can affect the clinical outcome in patients. Like CVD, DM is also an inhibiting factor for improvement in COVID-19 patients with RDV therapy. Thus, DM is a comorbid COVID-19 that can be a predictor of acute lung damage and ARDS through an increase in ROS, IL-6, Inflammatory cytokines, and lipopolysaccharides that cause pulmonary fibrosis resulting in acute lung damage and ARDS. The two other potential mechanisms are the increased ROS production and the RAAS (renin-angiotensin-aldosterone system) activation by the viral. The increased angiotensin II expression results in insulin resistance, hyperglycemia, and damage to the endothelium of the vascular system. These all lead to CVD (cardiovascular disease), thromboembolism, DIC (disseminated intravascular coagulation), and mortality.[19]

Based on Table 3, obesity shows an increase the mortality (OR=17.513). Yu et al conducted a study on obese patients infected with COVID-19) in 43 hospitals in the US and found that obese patients decreased the likelihood of the length of stay (LOS) to less than 28 days compared to non-obese COVID-19 patients (*P*<0.001). However, this study shows that obesity is not significantly associated with mortality during 28 days of treatment.[20] Some studies related to obesity and COVID-19 also reveal that obesity significantly results in worse clinical outcomes and even has a higher risk factor for death than patients with average weight.[21–23]

In a study conducted in Istanbul, Sahin et al discovered that COVID-19 patients with average weight had lower levels of biomarkers of acute inflammation than obese patients did. Obesity was also identified as an independent predictor for the severity of COVID-19. In this cross-sectional investigation, obese patients frequently had pulmonary and hypoxic conditions. Besides, the hospitalization rate, the longer length of stay, the longer duration of ICU care, and the need for NIMV are more common in obese COVID-19 patients.[23]

According to the analysis, blood type O has the best chance of enhancing patients' clinical outcomes. The percentage of improvement in RDV therapy in patients infected with COVID-19 with blood type O (66.7%) is higher than other types (51.1%) with OR=1.917. This result indicates that RDV antiviral therapy in infected COVID-19 patients with blood type O is 1.917 times more effective in improving clinical outcomes than other types. The findings of several studies on the relationship between blood type and COVID-19 are compatible with this; for instance, Shibeeb et al and Zhao et al demonstrate that blood type O reduces the probability of infection and has milder symptoms than other blood types.[9,24]

This becomes one of the reasons that blood type O has the best chance of improving the clinical outcome. Considering that the sample size used in this study was relatively limited, further research is required on blood type's influence on the effectiveness of RDV therapy.

According to the statistical information in Table 2, the COVID-19 patients who are receiving RDV with variation blood type A (68.2%) also have a high proportion of improvement compared to those who have not improved (no improvement) with OR=1.866 (95% CI=0.633-5.254; *P*=0.313). Thus, it indicates that RDV antiviral therapy in infected COVID-19 patients with blood type A has 1.866 times more effective in improving clinical outcomes. Despite increasing the risk for COVID-19 infection, blood type A did not significantly impact the high degree of symptom severity.[25] Zietz et al explain that although type A increases the chance of getting COVID-19 infection, it also reduces the risk of being intubated. (ARD = -2.9; 95% CI=7.2–0.6) and death (ARD = -1.6; 95% CI=4.9–1.6).[10,26]

Different from blood types O and A, blood types B (40.0%) and AB (30%) have a low percentage of improvement compared to no improvement percentage. The highest mortality percentage is found in COVID-19 patients with blood type AB (30.0%), followed by type B (26.7%), type A (13.6%), and type O (12.1%). In a study conducted in New York, Zietz et al discovered that people with blood type AB had a high risk of mortality (ARD=1.4; 95% CI=6.9–8.9) and intubation (ARD=1.8; 95% CI=8.3–12.2) than other blood types. However, blood type B had a higher risk of intubation than other blood type variations (ARD=2.5; 95% CI=2.7–7.5).[10]

LIMITATIONS

The limitations in this study include the limited literature on the results of previous studies which were still small. Thus, this research has many weaknesses, both in terms of research results and analysis. In addition, there is also a limited number of samples, which was only 80 patients. Thus, further research is needed to see how variations in blood type have different effects on the effectiveness of Remdesivir.

CONCLUSION

Blood type variation significantly affects the effectiveness of RDV antiviral therapy (OR=1.705; 95% CI=1.091–2.665; *P*=0.019) based on the WHO Clinical Progression Scale. However, when influenced by other confounding variables, blood type variation does not significantly affect the effectiveness of RDV antiviral therapy (OR=1.320; 95% CI=0.751–2.319; *P*=0.334). RDV therapy in infected COVID-19 patients with blood types A and O has better effectiveness in improving the clinical outcome compared to other blood types. The sample size used in this study might have certain limitations. Therefore, more studies are required to determine how blood type affects the effectiveness of RDV therapy.

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CONFLICT OF INTEREST

The authors acknowledge that there are no substantial conflicting interests, such as financial, professional, or personal interests, which may

influence how the work reported in this publication is performed or presented.

AVAILABILITY OF DATA AND MATERIALS

On reasonable request, the corresponding author would provide you with the data and materials to support the findings of this study.

AUTHORS' CONTRIBUTION

The study was conceived and designed by EV, RA, NF, and AW. The data were gathered, examined, and interpreted by EV. The manuscript was written by EV, RA, NF, and AW. The final draft of the work was approved by all authors after a critical revision for significant intellectual substance.

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