



# Clinical Outcome of Antiviral Therapy on COVID-19 Patients

Gestina Aliska<sup>1,2\*</sup>, Andani Eka Putra<sup>3</sup>, Ricvan Dana Nindrea<sup>4</sup>, Widy Nur Utami<sup>5</sup>, SM Rezvi<sup>6</sup>

<sup>1</sup>Department of Clinical Pharmacology, Dr. M Djamil General Hospital, West Sumatra, Indonesia; <sup>2</sup>Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Andalas, West Sumatra, Indonesia; <sup>3</sup>Department of Microbiology, Faculty of Medicine, Universitas Andalas, West Sumatra, Indonesia; <sup>4</sup>Department of Education and Research, Dr. M Djamil General Hospital, Padang, Indonesia; <sup>5</sup>Pharmacy and Therapeutics Committee, Dr. M Djamil General Hospital, West Sumatra, Indonesia; <sup>6</sup>Magister of Biomedical Programme, Faculty of Medicine, Universitas Andalas, West Sumatra, Indonesia

## Abstract

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**\*Correspondence:** Gestina Aliska, Faculty of Medicine, Universitas Andalas, Jalan Perintis Kemerdekaan No. 94, Padang 25127, West Sumatera, Indonesia. E-mail: aliska@med.unand.ac.id

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**BACKGROUND:** A novel coronavirus-caused pneumonia has been widespread worldwide since the end of 2019. The rapid widespread has prompted the repurposing of drugs based on promising *in vitro* and therapeutic results with other human coronavirus diseases. These repurposed drugs have mainly included remdesivir, favipiravir, lopinavirritonavir, ribavirin, interferons, and hydroxychloroquine.

**AIM:** This study aims to evaluate the efficacy of any antiviral for 2019-nCoV infection in a national referral hospital.

**METHODS:** This research was a retrospective study to evaluate all antiviral clinical responses used in a national referral hospital.

**RESULTS:** Based on gender, there is a similar frequency from all patients. Hematology, followed by cardiovascular and pulmonary disease, is the most frequent comorbidity. There is no significant difference between the two groups antiviral treatment for a length of stay parameter. The most extended length of stay is 29 days. About 64.5% of patients are cured of SARS-Cov-2 infection. In the remdesivir group, we find that the mortality is significantly high.

**CONCLUSION:** The clinical outcome of these antiviral treatments is similar, except for mortality. The severity of COVID-19 causes differences in mortality.

## Introduction

In December 2019, a novel coronavirus caused pneumonia in Wuhan, China [1]. About 110,749,023 people were confirmed as COVID-19 infection patients [2]. Rapid widespread of the disease has prompted the repurposing of drugs based on promising *in vitro* and therapeutic results with other human coronavirus diseases such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [3], [4]. These repurposed drugs have mainly included remdesivir, favipiravir, lopinavir-ritonavir, ribavirin, interferons, and hydroxychloroquine [4], [5]. Data from the WHO solidarity trial show that remdesivir, hydroxychloroquine, lopinavir, and interferon regimens slightly affected hospitalized COVID-19 patients for clinical outcomes such as overall mortality, initiation of ventilation, and duration of hospital stay [6].

The National Food and Drug Administration approved some antiviral drugs with emergency authorization in Indonesia, such as hydroxychloroquine, favipiravir, and remdesivir. In Indonesia, antiviral regimens in The National Programme for COVID-19

therapy were remdesivir and favipiravir. The evaluation of the efficacy of these drugs is still under-reported. This study aims to evaluate the efficacy of any antiviral for 2019-nCoV infection in a national referral hospital.

## Materials and Methods

This research was a cohort retrospective study to evaluate all antiviral clinical responses used in a national referral hospital. About 282 patients from October 2020 to April 2021 were included in this study as total sampling. Inclusion criteria were adult patients who received antiviral therapy. We analyzed clinical outcomes based on the mortality rate, length of stay, and time to conversion. The Ethics Commission of Dr. M. Djamil General Hospital approved the ethical clearance of this study with number 135/KEPK/2021.

Initial investigations included a complete blood count, coagulation profile, and serum biochemical test (including renal function, liver function, and blood gas

analysis). Nasal and pharyngeal swabs were tested for SARS-CoV using real-time RT-PCR assays approved by the Indonesian Food and Drug Administration. Routine bacterial examinations from the sputum were also performed.

**Table 1: Patient's characteristics**

	All patients (n = 282)	Favipiravir (n = 171)	Remdesivir (n = 111)
<b>Gender</b>			
Male (n,%)	154 (54.6)	83 (48.5)	71 (64)
Female (n,%)	128 (45.4)	88 (51.5)	40 (36)
Age (mean, SD)	56 (17-92)	49 (17-92)	63 (23-83)
<b>Comorbidities</b>			
Cardiovascular (%)	126/282 (44.7)	76/171 (44.4)	50/111 (45)
Endocrine (%)	91/282 (32.3)	40/171 (23.4)	51/111 (45.9)
Pulmonary disease (%)	121/282 (42.9)	39/171 (22.8)	82/111 (73.9)
Hematology (%)	144/282 (51.1)	80/171 (46.8)	64/111 (57.7)
Others (%)	105/282 (37.2)	69/171 (40.4)	36/111 (32.4)
<b>Oxygen support</b>			
NRM (%)	103 (36.5)	43/171 (25.1)	60/111 (54.1)
HFNC (%)	76 (27)	6/171 (3.5)	70/111 (63.1)
Mechanical ventilator (%)	61 (21.6)	3/171 (1.8)	58/111 (52.3)
<b>Ct value at first diagnosed</b>			
< 25 (%)	31 (33.7)	27/70 (38.6)	4/22 (18.2)
25–30 (%)	29 (31.5)	19/70 (27.1)	10/22 (45.5)
>30 (%)	32 (34.8)	24/70 (34.3)	8/22 (36.4)
<b>Others drug therapy</b>			
ACE-I (%)	17 (6)	13/171 (7.6)	4/111 (3.6)
ARB (%)	52 (18.4)	35/171 (20.5)	17/111 (15.3)
Anticoagulant (%)	170 (60.3)	100/171 (58.5)	70/111 (63.1)
Statin (%)	25 (8.9)	16/171 (9.36)	9/111 (8.1)
<b>Severity</b>			
Critical (%)	82/282 (29.1)	4/171 (2.3)	78/111 (70.3)
Severe (%)	59/282 (20.9)	28/171 (16.4)	31/111 (27.9)
Moderate (%)	117/282 (41.5)	115/171 (67.3)	2/111 (1.8)
Mild (%)	24/282 (8.5%)	24/171 (14.0)	0/111 (0)

Given the emergence of COVID-19 pneumonia, antibiotics (orally and intravenously) were empirically administered. Antiviral therapy with, Favipiravir or Remdesivir, was given after being confirmed as COVID-19 after twice RT-PCR examination. As an anti-inflammation regimen, corticosteroid therapy (dexamethasone 6 mg/day) was given. Oxygen support (e.g., high flow nasal cannula and mechanical ventilation) was administered to patients based on hypoxemia severity.

The severity level of COVID-19 was assessed based on clinical data such as clinical symptoms, presence of pneumonia, and respiratory distress.

Repeated tests for RT-PCR were done to confirm viral clearance before hospital discharge. This data was used to calculate the time to conversion. The evaluation of intrahospital mortality and length of stay was also calculated from the medical record database. The data of viral load are expressed in the Ct value, which is classified by high viral (Ct < 25), medium viral (Ct 25–30), and low viral load (Ct > 30) [7].

### Statistical analysis

Data were analyzed statistically based on variables assessed using a computerized system that is univariate and bivariate analysis. Univariate analysis was performed to see the frequency distribution of variables. Bivariate analysis is performed to analyze the relationship between the independent and dependent variables. Length of stay and time to conversion were analyzed with the Mann–Whitney U-test. The discharge

condition was analyzed with the Chi-square test. Statistical significance was accepted as  $p < 0.05$ .

## Results

Based on gender, there was a similar frequency from all patients. Between antiviral therapy, we found that the age was similar. The highest comorbidity was hematology, followed by cardiovascular and pulmonary disease. Many patients had more than one comorbidity. The distribution of viral load was similar between groups. Besides antiviral, almost all of these patients received anticoagulant therapy. Favipiravir was used mainly for moderate-to-severe cases, and the other side remdesivir was used for severe to critical cases (Table 1).

We find that WBC counts were varied in both groups of antiviral treatment. Almost all patients in our study had an abnormality of D-dimer. Between these two antiviral treatments, the abnormality of D-dimer was higher in the remdesivir group than favipiravir (Table 2).

**Table 2: Laboratory findings of patients with COVID-19**

	Normal range	All patients (n = 171)	Favipiravir (n = 171)	Remdesivir (n = 111)
WBC counts $\times 10^3/L$	5–10	8.5 (1–90.6)	6.9 (3.6–90.6)	11.4 (3.3–40.6)
Platelet count $\times 10^2/L$	150–400	251 (1–3370)	251 (4–3370)	236 (93–547)
D-dimer, ng/mL	< 500	1250.5 (135–10000)	842.5 (135–9368)	3396 (227–10000)
Normal (n,%)		49/282 (17.4)	43/171 (24.1)	6/111 (5.4)
Abnormal (n,%)		233/282 (82.6)	128/171 (74.9)	105/111 (94.6)
SGOT, U/L (n = 233)	< 38	35 (8–2057)	29 (8–287)	48 (11–2057)
Normal (n,%)		126/233 (54.1)	90/135 (66.7)	36/98 (36.7)
Abnormal (n,%)		107/233 (45.9)	45/135 (33.3)	62/98 (63.3)
SGPT $\times U/L$ (n = 234)	< 41	31 (2–1753)	28 (2–210)	36 (8–1753)
Normal (n,%)		158/234 (67.5)	103/136 (75.7)	55/98 (56.1)
Abnormal (n,%)		76/234 (32.5)	33/136 (24.3)	43/98 (43.9)
Ureum, mg/dL	10–50	29 (1–376)	20 (7–376)	50 (9–259)
Creatinine, mg/dL	0.8–1.3	0.9 (0.4–490.7)	0.8 (0.4–490.7)	0.9 (0.4–5.4)

Parameter for clinical outcomes was assessed from the length of stay, time to conversion, and intrahospital mortality. There was no significant difference between the two groups antiviral treatment for a length of stay parameter. The most extended length of stay was 29 days. About 64.5% of patients were cured of SARS-Cov-2 infection. In the remdesivir group of treatment, we find that the mortality is significantly high (Table 3).

**Table 3: Clinical outcome of patients with COVID-19**

Clinical Outcomes	All patients	Favipiravir	Remdesivir	p value
Length of stay (n = 282)	11.8 (1–29)	11 (1–27)	10 (1–29)	$p = 0.125$
Time to conversion (n = 256)	10 (2–28)	10 (2–28)	10 (2–20)	$p = 0.533$
Discharge condition (n = 282)				$p < 0.001$
Cured (n,%)	182 (64.5)	151 (88.3)	31 (27.9)	
Died (n,%)	100 (35.5)	20 (11.7)	80 (72.1)	

## Discussion

Among 282 patients with median age was 56 (interquartile range, 17–92 years), we find

mortality about 35.5%. Most of them received remdesivir therapy. Our finding showed that patients with mechanical ventilators lead died in remdesivir therapy. Although the other study reported that remdesivir treatment led to a decrease in the high-risk COVID-19 state (the use of mechanical ventilators) by 34.8% (95% CI 26.7–42.0%) for 14 days and 29.3% (95% CI 28.8–29.8%) up to 28 days, which were reduction of death by 30.5% (95% CI 6.6, 50.9%) up to 28 days [8], [9]. Remdesivir therapy for patients with low-risk state showed the efficacy in reducing subsequent progression to high-risk state and death by 26% (relative rate (RR), 0.74; 95% CI, 0.55–0.93) and 62% (RR, 0.38; 95% CI, 0.29–0.48), respectively. Less but still statistically significant efficacy in mortality reduction was noted for the medium- and high-risk patients [10].

Garibaldi *et al.* analyzed that 342 patients with remdesivir therapy with the median age were 60 years (interquartile range, 46–69 years), and 189 (55.3%) were men. Remdesivir recipients had a shorter time to clinical improvement than matched controls without remdesivir treatment (median, 5.0 days [interquartile range, 4.0–8.0 days] versus 7.0 days [interquartile range, 4.0–10.0 days]; adjusted hazard ratio, 1.47 [95% CI, 1.22–1.79]). Remdesivir recipients had a 28-day mortality rate of 7.7% (22 deaths) compared with 14.0% (40 deaths) among matched controls, but this difference was not statistically significant in the time-to-death analysis (adjusted hazard ratio, 0.70; 95% CI, 0.38–1.28) [11].

The other studies with overall 174 patients were used, out of which 71 (40.80%) received remdesivir. It reported no significant difference in deaths between patients who received remdesivir and patients who did not receive remdesivir ( $p = 0.122$ ). Although, the length of stay was significantly lower in the remdesivir group than in the control group ( $p = 0.001$ ) [12]. In this study, some patients had rapidly worsening conditions, with the length of stay just 1 day.

This study has several limitations, that why the result must be interpreted carefully. The data were collected from the medical record without matching control. We just analyzed the difference between the two antiviral treatments. It was a retrospective study; thus, some important variables were not assessed, such as time of death and time to clinical response. The sample size is minimal, and data were used from one tertiary care hospital. Therefore, this data is hard to generalize. In the future, prospective studies should be conducted in multicenter and assess the efficacy of antiviral that might reduce mortality rate and clinical outcomes in patients with any severity of COVID-19.

## Conclusions

The clinical outcome of these antiviral treatments is similar, except for mortality. The severity of COVID-19 causes differences in mortality.

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