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EFEKTIVITAS TERAPI ANTIVIRUS COVID-19 DAN HUBUNGANNYA DENGAN VAKSINASI: ANALISIS RETROSPEKTIF

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Abstrak

Latar belakang: *COVID-19 diketahui telah menginfeksi lebih dari jutaan orang. Pengobatan untuk COVID-19 dapat menggunakan antivirus, seperti remdesivir dan favipiravir. Selain antivirus, vaksinasi menjadi salah satu strategi untuk menekan penyebaran COVID-19. Penelitian ini bertujuan untuk menganalisis efektivitas antivirus serta hubungan vaksinasi terhadap efektivitas terapi kedua antivirus tersebut pada pasien COVID-19 berdasarkan perbaikan kondisi klinis pasien, lama rawat inap dan mortalitas.*

Metode: *Penelitian ini menggunakan desain kohort retrospektif yang dilakukan di Rumah Sakit Universitas Indonesia, Depok, Indonesia. Data diambil dari data rekam medis dan database rumah sakit periode Januari 2021 - Agustus 2022. Antivirus dalam penelitian ini adalah remdesivir dan favipiravir. Sampel dibagi menjadi dua kelompok, yaitu kelompok yang divaksinasi dan tidak divaksinasi.*

Hasil: *Faktor yang mempengaruhi efektivitas terapi remdesivir dan favipiravir adalah derajat keparahan COVID-19 serta menunjukkan bahwa vaksinasi memberikan pengaruh yang signifikan terhadap perbaikan kondisi klinis, penurunan lama rawat inap dan mortalitas pada pasien yang diobati dengan remdesivir dan telah divaksinasi dibandingkan dengan yang belum divaksinasi. Dan pada pasien yang mendapat terapi favipiravir dan divaksinasi juga menunjukkan efek perbaikan kondisi klinis, lama rawat inap dan mortalitas dibandingkan dengan pasien yang tidak divaksinasi, meskipun hasilnya tidak signifikan secara statistik.*

Kesimpulan: *Vaksinasi berpengaruh positif terhadap efektivitas remdesivir dan favipiravir pada pasien COVID-19 yaitu dapat memperbaiki kondisi klinis pasien kearah yang lebih baik, mengurangi lama rawat inap dan kematian.*

Kata kunci: *COVID-19, efektivitas, remdesivir, favipiravir, vaksinasi*

EFFECTIVENESS OF COVID-19 ANTIVIRUS THERAPY AND ITS RELATIONSHIP WITH VACCINATION: A RETROSPECTIVE ANALYSIS

Abstract

Background: *COVID-19 is known has infected more than millions of people. COVID-19 can be treated with antivirals. Besides antiviral drugs, vaccination becomes one of the strategies to suppress the spread of COVID-19. This study aims to analyze the effectiveness of antivirus and the relationship between vaccination and the effectiveness of the two antiviral therapies in COVID-19 patients based on improvements in the patient's clinical condition, length of stay and mortality.*

Methods: *This study used a retrospective cohort design conducted at the Universitas Indonesia Hospital, Depok, Indonesia. Data have been taken from medical records and hospital databases from January 2021 - August 2022. The antivirals in this study were remdesivir and favipiravir. The samples was divided into two groups, namely the vaccinated and not vaccinated groups.*

Results: *The factors affecting the effectiveness of remdesivir and favipiravir therapy were the severity of COVID-19 and showed that vaccination had a significant effect on improving clinical conditions, reducing length of stay and mortality in patients treated with remdesivir and who had been vaccinated compared to those who had not been vaccinated. And in patients who received favipiravir therapy and were vaccinated, it also showed an effect on improving clinical conditions, length of stay and mortality compared to patients who were not vaccinated, although the results were not statistically significant.*

Conclusion: *Vaccination has a positive effect on the effectiveness of remdesivir and favipiravir in COVID-19 patients, which can improve the patient's clinical condition towards a better direction, reduce length of hospitalization and mortality.*

Keywords: *COVID-19, effectiveness, remdesivir, favipiravir, vaccination*

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has rapidly spread as a pandemic and it has infected more than 1 million people worldwide.[1] The clinical manifestations of COVID-19 is broad and can range from mild illness to critical illness.[2] Common symptoms include fever, cough, shortness of breath, anosmia, headache, skin symptoms, and others. Such clinical manifestations can be bad in some patients with other diseases and in the elderly.[3] Thus, comprehensive steps must be taken to resolve the pandemic optimally starting from preventive to curative measures. Improper treatment should be addressed to help reduce infection cases and death.[4]

Several potential antivirals drugs that can be used to treat COVID-19 have been tested and recommended in several countries, including Indonesia.[5] Remdesivir is a nucleoside analogue that is known to inhibit the replication of SARS-CoV-2.[6] Data on the effectiveness of remdesivir are varied. A retrospective study of health systems showed that remdesivir reduced hospital stay and showed good clinical improvement in 342 recipients, but did not reduce mortality.[7] However, another retrospective study of 28.555 patients showed a decrease in mortality at days 14 and 28.[8] Meanwhile, favipiravir is an oral drug with a broad-spectrum.[3] Data on the effectiveness of favipiravir are limited. An Randomized Control Trial (RCT) study found that the combination of favipiravir and interferon-alfa treated SARS-CoV-2 infection more quickly than other combination therapy.[9] Another open label study using a prospective RCT design found no significant difference in clinical recovery rates at day 7.[10]

Besides antiviral drugs, vaccination becomes one of the strategies used to suppress the spread of COVID-19. Vaccination is known to significantly reduce symptoms of COVID-19 in elderly patients and increase protection against serious illness.[11] Vaccines are known to affect reducing disease severity, length of stay, and mortality.[12] Moreover, vaccination provides a significant reduction in the average length of stay, ICU needs, mortality & medical costs in patients compared to those who are not vaccinated.[13] Although it has many benefits, it turns out that there are still cases of post-vaccination COVID-19 infection, especially in Indonesia.[14,15] This has resulted in various perceptions in the community regarding the COVID-19 vaccine.

To drugs that are used in in a pandemic era, monitoring the effectiveness of the therapy is important.[16] The effectiveness of remdesivir and favipiravir has been studied both in Indonesia and in other countries. However, the effect of vaccination on the effectiveness of these two drugs in COVID-19 patients has not been proven. Therefore, this study aims to analyze the effectiveness of remdesivir and favipiravir and the relationship of vaccination on the effectiveness of both antiviral therapy in COVID-19 patients based on improvements in the patient's clinical condition, length of stay and mortality at the University of Indonesia Hospital, Depok, Indonesia.

METHOD

Study Design and Population

This observational study used a retrospective cohort design and it was conducted at the University of Indonesia Hospital, Depok, Indonesia. The effectiveness of remdesivir and favipiravir therapy was assessed based on the clinical improvement using the WHO clinical progression score covering a scale of 0 (not infected) to 10 (dead), length of stay, and mortality. The ethical approval of this study was obtained from the Ethics Committee of the Universitas Indonesia Hospital (number: S-037/KETLIT/RSUI/VIII/2022).

The population of this study consisted of inpatients at the Universitas Indonesia Hospital who had confirmed COVID-19. Inclusion criteria for this study were patients over 18 years of age with mild, moderate or critical severity, patients with and without comorbidities, and patients taking remdesivir and favipiravir therapy. This study excluded patients with incomplete medical record data, patients who had changed or use two antivirals during treatment, patients who were discharged at their request, and were referred to another hospital. The minimum sample for each group is 45 subjects. The

determination of the sample used a consecutive sampling.

In this study, comparisons were made by assessing the vaccine (patients receiving COVID-19 vaccination) and non-vaccine (patients who have not been COVID-19 vaccination) groups based on the value of clinical improvement, length of stay, and the numbers of mortality. Improvement in the patient's clinical condition 14 days after the therapy was based on the WHO clinical progression score.[17,18] It is said that there is an improvement if there is a decrease in the score of at least 2 after 14 days of therapy.[7] This clinical condition assessment was based on the doctor's assessment recorded in the medical record. The endpoint of the observation was the 14th day after antiviral therapy calculated starting from the first day of the administration of the therapy to patients. The length of stay is the number of days the patient is hospitalized which is calculated from the first day of admission to the hospital until the day the patient is discharged. And for mortality, it is assessed based on the patient's condition when discharged from the hospital, whether alive or dead.

This study categorized age according to WHO group. The research subjects were adult (≥ 18 years) and elderly patients (60 years) which is an age group that is at risk of having a worsening condition due to COVID-19[19], and associated with low immune function and increased mortality.[20] Meanwhile, gender was clasified into male and female. Comorbidities are divided into no comorbidities and comorbidities because comorbidities are associated with lower immune function,[20] severity and mortality of COVID-19 patients.[21] The body mass index (BMI) category is classified into underweight-normal (<18.5 - ≤ 24.9) and overweight-obese (25 - ≥ 30).[20,22] The severity categories are based on the 4th edition of the COVID-19 management guidelines, that is mild, moderate, and severe/critical.[5] All covariates were thought to be confounding variables on improvement in clinical condition, length of stay, and mortality.

Data Collection and Analysis

Data were taken from medical records and hospital databases from January 2021 to August 2022. Data covered demographics, co-morbidities, history of antiviral therapy (type of antiviral and time of administration of antiviral), vaccination status (already vaccinated COVID-19 or not), clinical results (patient condition 14 days after the therapy), and polymerase chain reaction (PCR) test results. Data analysis using the statistical software IBM SPSS, version 23. Data were analyzed using descriptive analysis to describe patient demographic information and patient's clinical condition status. Categorical data are presented as proportions (%) and numerical data are presented as mean ± SD. Bivariate analysis was used the Chi-square test, to analyze the effect of vaccination and other variables on improving the patient's clinical condition, length of stay, and mortality of patients receiving remdesivir or favipiravir.

RESULTS

Demographic characteristics

This study evaluated a total of 275 medical records of patients receiving remdesivir. This number consisted of two groups, vaccine groups (105 patients) and non-vaccine groups (170 patients) who met the predetermined criteria (Table 1). The average age of the patients was 56.01 ± 15.68. Most of the patients in both groups were adults, had a history of co-morbidities and had more than 1 co-morbidity. The average body mass index (BMI) was 25.71 ± 6.10. In the vaccine group, the majority were female patients (50.5%) with the BMI category of <18.5 - <24.9 (thin to normal) with a total of 55 patients (52.4%). Then, the degree of disease severity is mild/moderate (79.0%). Meanwhile, in the non-vaccine group, the majority were male patients (54.1%), with the most BMI categories of overweight to obesity with a total of 86 patients (50.6%) with a severe/critical degree of severity (74.7%).

This study evaluated a total of 133 patients receiving favipiravir therapy. This number consisted of vaccine groups (47 patients who had been vaccinated) and non-vaccine groups (86 patients who had not been vaccinated). In general, the characteristics of the patients were quite similar for

vaccine and non-vaccine group (Table 1). Most of the patients in both groups were adult patients with an average age of 49.33 ± 16.72, female, had a history of comorbidities, had more than 1 comorbidity with mild/moderate severity, and an average BMI of 25.77 ± 5.47. In the vaccine group, most of the patients had a thin to normal BMI of 28 (59.6%), while the majority in the non-vaccine group had an overweight to obese BMI, that is 151 (59.3%).

Tabel.1 Characteristics of COVID-19 patients receiving remdesivir and favipiravir theraphy based on vaccination status

Patient characteristics	Category	Remdesivir		Favipiravir	
		Vaccine (n=105)	Non vaccine (n=170)	Vaccine (n=47)	Non vaccine (n=86)
		n (%)	n (%)	n (%)	n (%)
Age	Mean±SD	56.01 ± 15.68		49.33 ± 16.72	
	Adult (18-59 years)	65 (61.9)	92 (54.1)	37 (78.7)	59 (68.6)
	Elderly (>59 years)	40 (38.1)	78 (45.9)	10 (21.3)	27 (31.4)
Gender	Male	52 (49.5)	92 (54.1)	17 (36.2)	38 (44.2)
	Female	53 (50.5)	78 (45.9)	30 (63.8)	48 (55.8)
History of comorbidities	No	14 (13.3)	15 (8.8)	10 (21.3)	25 (29.1)
	Yes	91 (86.7)	155 (91.2)	37 (78.7)	61 (70.9)
Number of comorbidities	None	14 (13.3)	15 (8.8)	10 (21.3)	25 (29.1)
	1 Comorbid	23 (21.9)	25 (14.7)	14 (29.8)	26 (30.2)
	>1 Comorbidities	68 (64.8)	130 (76.5)	23 (48.9)	35 (40.7)
BMI	Mean±SD	25.71 ± 6.10		25.77 ± 5.47	
	Thin-Normal	55 (52.4)	84 (49.4)	28 (59.6)	35 (40.7)
	Overweight-Obese	50 (47.6)	86 (50.6)	19 (40.4)	51 (59.3)
Degree of severity	Mild/moderate	83 (79.0)	43 (25.3)	46 (97.9)	85 (98.8)
	Severe/critical	22 (21.0)	127 (74.7)	1 (2.1)	1 (1.2)

Table.2 The relationship between vaccination and the effectiveness of remdesivir and favipiravir therapy

Outcome	Category	Remdesivir			Favipiravir		
		Vaccine (n=105)	Non vaccine (n=170)	p-value	Vaccine (n=47)	Non vaccine (n=86)	p-value
		n (%)	n (%)		n (%)	n (%)	
Clinical condition improvement	Improve	94 (89,5)	91 (53,5)	0,000	46 (97.9)	78 (90.7)	0.158
	Worsen	11 (10,5)	79 (46,5)		1 (2.1)	8 (9.3)	
Length of stay	1-14 days	90 (85,7)	101 (59,4)	0,000	45 (95.7)	81 (94.2)	1.000
	>14 days	15 (14,3)	69 (40,6)		2 (4.3)	5 (5.8)	
Mortality	No	95 (90.5)	114 (67.1)	0.000	46 (97.9)	83 (96.5)	1.000
	Yes	10 (9.5)	56 (32.9)		1 (2.1)	3 (3.5)	

The assessment of the effectiveness of therapy is based on the clinical condition improvement in the patient's, length of stay, and mortality of the COVID-19 patients (Table 2). A total of 89.5% of patients who were treated with remdesivir in the vaccine group experienced an improvement in clinical condition compared to those in the non-vaccine group (OR=0.135; 95% CI=0.067-0.270, p-value=0.000). Then, as many as 85.7% of patients receiving remdesivir therapy in the vaccine group had a length of stay of 1-14 days, while 14.3% of those in the non-vaccine group had a length of stay <14 days (OR=0.244; 95% CI=0.130-0.456, p-value=0.000). In terms of the mortality parameter, 90.5% of patients receiving remdesivir therapy in the vaccine group did not die compared to the non-vaccine group (OR=0.214; 95% CI=0.101-0.443, p-value=0.000). And for patients who were given favipiravir therapy, it was found that 97.9% of patients in the vaccine group experienced better clinical conditions than those in the non-vaccine group but not statistically significant (OR=0.212; 95%

CI=0.026-1.749, p-value=0.158). In terms of the length of stay, the results showed that 95.7% of patients in the vaccine group had a length of stay of 1-14 days, while 4.3% of the patients in non-vaccine group 4 had a length of stay of < 14 days but not statistically significant (OR=0.720; 95% CI=0.134-3.863, p-value=1.000). For the mortality parameter, the results showed that 97.9% of patients in the vaccine group do not die even though it is not statistically significant (OR=0.601; 95% CI=0.061-5.949, p-value=1,000).

Table. 3 Factors affecting the effectiveness of remdesivir therapy

Risk Factor	Category	Clinical condition improvement		p-value	Length of stay		p-value	Mortality		p-value
		Improve	Worsen		1-14 days	>14 days		No	Yes	
		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Age	Adult (18-59 years)	109 (69,4)	48 (30,6)	0,436	108 (68,8)	49 (31,2)	0,793	128 (81.5)	29 (18.5)	**0,015**
	Elderly (>59 years)	76 (64,4)	42 (35,6)		83 (70,3)	35 (29,7)		81 (68.6)	37 (31.4)	
Gender	Male	89 (61,8)	55 (38,2)	0,053	92 (63,9)	52 (36,1)	**0,037**	104 (72.2)	40 (27.8)	0,157
	Female	96 (73,3)	35 (26,7)		99 (75,6)	32 (24,4)		105 (80.2)	26 (19.8)	
Comorbidity	No	23 (79,3)	6 (20,7)	0,208	21 (72,4)	8 (27,6)	0,833	29 (100.0)	0 (0.0)	**0,000**
	Yes	162 (65,9)	84 (34,1)		170 (69,1)	76 (30,9)		180 (73.2)	66 (26.8)	
BMI	Thin-Normal	96 (69,1)	43 (30,9)	0,607	101 (72,7)	38 (27,3)	0,295	109 (78.4)	30 (21.6)	0,397
	Overweight-Obese	89 (65,4)	47 (34,6)		90 (66,2)	46 (33,8)		100 (73.5)	36 (26.5)	
Degree of severity	Mild/moderate	110 (87,3)	16 (12,7)	**0,000**	116 (92,1)	10 (7,9)	**0,000**	112 (88.9)	14 (11.1)	**0,000**
	Severe/critical	75 (50,3)	74 (49,7)		75 (50,3)	74 (49,7)		97 (65.1)	52 (34.9)	

In this study, it was found that the severity of COVID-19 was a risk factor that significantly influenced the clinical condition improvement of COVID-19 patients who were given remdesivir therapy with a p-value <0.05, which was 87.3% of patients with mild severity/ were experiencing better clinical condition improvement and as many as 50.3% of patients with severe/critical severity had improved clinical condition (OR=0.147; 95% CI=0.080-0.273, p-value=0.000). On the length of stay parameter, the results obtained were that of gender (OR=0.572; 95% CI=0.339-0.966, p-value=0.037) and the degree of severity of COVID-19 (OR=0.087; 95% CI=0.042-0.180, p-value=0.000) is a risk factor that significantly affects the length of stay of COVID-19 patients who are given remdesivir therapy with a p value <0.05 (Table 3). And in terms of the mortality parameter, it is known that age, comorbidities and disease severity are risk factors that significantly affect mortality in COVID-19 patients who are given remdesivir therapy with a p value <0.05. It is known that 81.5% of adult patients (OR=2.016; 95% CI=1.152-3.530, p-value=0.015), 100% of patients who have no comorbidities and 88.9% of patients with mild / moderate severity (OR= 0.233; 95% CI = 0.122-0.447, p-value = 0.000) did not experience mortality.

The risk factor that significantly affected the clinical condition improvement of patients receiving favipiravir therapy was the degree of severity with a p-value of <0.05, as many as 94.7% of patients with mild/moderate severity experienced improvement in clinical conditions towards a better direction and in severe/critical severity there were no patients who experienced improvement in clinical conditions. There are no risk factors that significantly affect the length of stay of COVID-19 patients receiving favipiravir. The risk factor for disease severity is a factor that significantly affects mortality in COVID-19 patients receiving favipiravir therapy with a p-value of <0.05. It is known that 98.5% of patients with mild/moderate severity do not experience mortality (Table 4).

Table. 4 Factors affecting the effectiveness of favipiravir therapy

Risk Factor	Category	Clinical condition improvement		p-value	Length of stay		p-value	Mortality		p-value
		Improve	Worsen		1-14 days	>14 days		No	Yes	
		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Age	Adult (18-59 years)	92 (95.8)	4 (4.2)	0,115	93 (96.9)	3 (3.1)	0,094	95 (99.0)	1 (1.0)	0,065
	Elderly (>59 years)	32 (86.5)	5 (13.5)		33 (89.2)	4 (10.8)		34 (91.9)	3 (8.1)	
Gender	Male	51 (92.7)	4 (7.3)	1,000	51 (92.7)	4 (7.3)	0,447	53 (96.4)	2 (3.6)	1,000
	Female	73 (93.6)	5 (6.4)		75 (96.2)	3 (3.8)		76 (97.4)	2 (2.6)	
Comorbidity	No	34 (97.1)	1 (2.9)	0,444	34 (97.1)	1 (2.9)	0,675	35 (100.0)	0 (0.0)	0,573
	Yes	90 (91.8)	8 (8.2)		92 (93.9)	6 (6.1)		94 (95.9)	4 (4.1)	
BMI	Thin-Normal	59 (93.7)	4 (6.3)	1,000	60 (95.2)	3 (4.8)	1,000	62 (98.4)	1 (1.6)	0,621
	Overweight-Obese	65 (92.9)	5 (7.1)		66 (94.3)	4 (5.7)		67 (95.7)	3 (4.3)	
Degree of severity	Mild/moderate	124 (94.7)	7 (5.3)	**0,004**	125 (95.4)	6 (4.6)	0,103	129 (98.5)	2 (1.5)	**0,001**
	Severe/critical	0 (0.0)	2 (100.0)		1 (50.0)	1 (50.0)		0 (0.0)	2 (100.0)	

DISCUSSION

Coronavirus disease 2019 (COVID-19), has turn into pandemic affecting more than one million people worldwide and is spreading very fast. [1,2] This requires a fast response from the government and health facilities. One of the efforts is to ensure the availability of safe and quality health services.[23] Another effort is the rapid development of treatment guidelines from health and community stakeholders so that infected and death can be reduced.[4] This study analyzed the effect between vaccination and the effectiveness of remdesivir and favipiravir as antivirals in COVID-19 patients. In this research, the effectiveness of remdesivir and favipiravir therapy was assessed from several categories: patient clinical condition improvement, length of stay, and patient mortality.

This study shows that the patient's vaccination status affects the increase in the effectiveness of remdesivir and favipiravir therapy. The COVID-19 patients receiving remdesivir therapy in the vaccine groups showed that the improvement in their clinical condition increased compared to those in the non-vaccine group (89.5% vs. 53.35%). Meanwhile, patients receiving favipiravir therapy in the vaccine group showed good clinical condition improvement compared to those in the non-vaccine group (97.9% vs. 90.7%) although not statistically significant. This is suitable with previous studies which found that vaccination and antivirals have a synergistic effect [24] and also that vaccination and administration of remdesivir in high-risk patients can prevent the clinical development of COVID-19 towards a more severe one.[25] Another study found that the use of remdesivir showed good improvement in clinical conditions.[7] There was also a study which showed that favipiravir therapy could increase clinical improvement at days 7 and 14, but this was not statistically significant.[9] Remdesivir and favipiravir is an RNA-dependent RNA polymerase (RdRP) inhibitor that is predicted to be able to treat severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[26,3] The clinical condition improvement of the patient's was assessed when antiviral therapy was first given for up to 14 days using the WHO clinical progression score. If there is a decrease in the score of at least 2 after 14 days of therapy, it is considered that there is clinical improvement.

This present study found that the degree of severity affected improvement in clinical conditions, length of stay and mortality. This is in line with previous studies that severity can affect the patient's recovery process.[27] Generally, the severity of COVID-19 is associated with systemic inflammation experienced by patients which can increase the risk of mortality.[28] Patients with mild COVID-19 lead to better clinical condition improvement, shorter lengths of stay, and a lower risk of mortality. This result is associated to the infection process of the SARS-

CoV-2, when the virus is still in the replication stage, it is expected that the use of antivirals will be more effective.[29] Remdesivir and favipiravir acts by inhibiting viral RdRp which can reduce viral replication rates.[30] Reduced viral load and good immune response mean that there is no inflammatory response in the body and this leads to clinical conditian improvement. The severity of the degree of COVID-19 is associated with an increase in the inflammatory reaction.[4]

The results of this study also show that the patient's vaccination status affects the reduction in the length of stay and mortality in COVID-19 patients receiving remdesivir or favipiravir therapy. The majority of patients receiving remdesivir therapy in the vaccine group had a relatively shorter length of stay between 1-14 days (85.7% vs. 59.4%) compared to those in the non-vaccine group (9.5% vs. 32.9%) and had lower mortality compared to patients who had not been vaccinated (9.5% vs. 32.9%). Moreover, patients receiving favipiravir therapy in the vaccine group had a shorter length of stay between 1-14 days (95.7% vs. 94.2%) and lower mortality (2.1% vs. 3.5%) than those in the non-vaccine group, but not significant. This result is consistent with previous studies that antiviral treatment combined with vaccination can be a strategic tool that can significantly reduce the length of stay and mortality [24] and it was also found that vaccination and remdesivir administration reduced hospitalization time and no intubation or death was reported.[25] Besides, other studies reveal that vaccination affects reducing the length of stay and mortality in COVID-19 patients.[12,13]

This study also reveals that vaccination can reduce the severity of disease in COVID-19 patients who had been vaccinated compared to those who have not been vaccinated. This is in line with research of Muhammed et al., that vaccines affect reducing the incidence of infection and disease severity.[12]

The main results of this study are that the vaccination has a good effect on the effectiveness of remdesivir and favipiravir therapy in patients with COVID-19 and there is a synergistic relationship between vaccination and antiviral treatment for clinical condition improvement and reduced length of stay, especially for severe to critical cases. This study can also be used as a reference in helping to formulate treatment guidelines, particularly for the Indonesian population to reduce the burden on public health. It is expected that it can increase public interest and awareness of vaccination. This study in helping to formulate treatment

As this study was only conducted in one hospital, the results cannot be generalized. However, this study can provide an description of the effect of vaccination on the effectiveness of remdesivir and favipiravir therapy in COVID-19 patients at the Universitas Indonesia Hospital, Depok, Indonesia. Moreover, the limited number of samples also affects the results obtained. Further studies can be carried out prospectively by considering some other variables and can be carried out in more than one location.

CONCLUSION

It can be concluded that the degree of severity of COVID-19 is a risk factor that can affect the effectiveness of COVID-19 antiviral therapy and vaccination has a positive effect on the effectiveness of remdesivir and favipiravir therapy in patients with COVID-19. In this case, vaccination and antiviral therapy can improve the clinical condition of patients, reduce the length of stay and mortality as well as reduce the severity of the disease. Besides, remdesivir and Favipiravir can be the right treatment alternative to cure COVID-19 patients. So that with proper treatment it is expected to reduce the burden on public health.

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