Original Article

Effectiveness of COVID-19 Antivirus Therapy and Its Relationship with Vaccination: A Retrospective Analysis

Andi Utari Prasetya Ningrum[1], Retnosari Andrajati[1,2], Nadia Farhanah Syafhan[1,2], Aditya Wirawan[3]

[1]Pharmacy Department, Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia
[2]Pharmaceutical Unit and Central Sterile Supply Department, Universitas Indonesia Hospital, Depok, Indonesia
[3]Department of Pulmonology and Respiratory Medicine, Universitas Indonesia Hospital, Depok, Indonesia

Abstract

Background: COVID-19 is known to have infected more than a million 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 aimed 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 were taken from medical records and hospital databases from January 2021 to August 2022. The antivirals in this study were remdesivir and favipiravir. The samples were divided into two groups, namely the vaccinated and unvaccinated groups.

Results: The factor affecting the effectiveness of remdesivir and favipiravir therapy was the severity of COVID-19. It was shown that vaccination had a significant effect on improving clinical conditions, reducing length of stay, and reducing mortality in patients treated with remdesivir who had been vaccinated compared to those who had not been vaccinated. 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 had a positive effect on the effectiveness of remdesivir and favipiravir in COVID-19 patients, which could improve the patient's clinical condition in a better direction, as well as reduce the length of hospitalization and mortality.

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

Corresponding Author:
Retnosari Andrajati | Pharmacy Department, Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia | andrajati@farmasi.ui.ac.id

Submitted: January 18th, 2021
Accepted: January 23rd, 2023
Published: July 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 195–203
https://doi.org/10.36497/jri.v43i3.434

Creative Commons Attribution-NonCommercial 4.0 International License

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has rapidly spread as a pandemic and has infected more than 1 million people worldwide.[1] The clinical manifestations of COVID-19 are broad and can range from mild to critical illness.[2] Common symptoms include fever, cough, shortness of breath, anosmia, headache, skin symptoms, and others. Such clinical manifestations can be critical in some patients with other diseases and 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 analog 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 indicated 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. A randomized control trial (RCT) study obtained that the combination of favipiravir and interferon-alfa treated SARS-CoV-2 infection more quickly than other combination therapies.[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 reduce disease severity, length of stay, and mortality.[12]

Moreover, vaccination provides a significant reduction in the mean length of stay, ICU needs, mortality, and medical costs of 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.

For drugs that are used 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 aimed to analyze the effectiveness of remdesivir and favipiravir, also the relationship between vaccination and the effectiveness of both antiviral therapies 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.

METHODS

This observational study used a retrospective cohort design and was conducted at the University of Indonesia Hospital, Depok, Indonesia. The effectiveness of remdesivir and favipiravir therapy was assessed based on 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 used two antivirals during treatment, patients who were discharged at their request, and patients who were referred to another hospital. The minimum sample for each group is 45 subjects. The determination of the sample used consecutive sampling.

In this study, comparisons were made by assessing the vaccine (patients receiving COVID-19 vaccination) and non-vaccine (patients who have not received COVID-19 vaccination) groups based on the value of clinical improvement, length of stay, and mortality numbers. 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 was the number of days the patient was hospitalized, which was calculated from the first day of admission to the hospital until the day the patient was discharged. Mortality was assessed based on the patient's condition when discharged from the hospital, whether alive or dead.

This study categorized age according to WHO groups. The research subjects were adults (≥18 years) and elderly patients (>59 years), which was an age group that was 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 categorized into male and female. Comorbidities were divided into no comorbidities and comorbidities, as comorbidities were associated with lower immune function,[20] higher severity, and higher mortality in COVID-19 patients.[21] The body mass index (BMI) category was classified

into underweight-normal (<18.5 to ≤24.9) and overweight-obese (25 to ≥30).[20,22] The severity categories were based on the 4th edition of the COVID-19 management guidelines: mild, moderate, and severe/critical.[23] All covariates were thought to be confounding variables for improvement in clinical condition, length of stay, and mortality.

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 antiviral administration), vaccination status (already vaccinated against COVID-19 or not), clinical results (patient's condition 14 days after the therapy), and polymerase chain reaction (PCR) test results.

Data analysis used the statistical software IBM SPSS, version 23. Data were analyzed using descriptive analysis to describe patient demographic information and the patient's clinical condition status. Categorical data were presented as proportions (%), and numerical data were presented as mean±SD. Bivariate analysis was used by applying 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

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. The mean 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 one co-morbidity (Table 1).

The mean 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 to <24.9 (thin to normal), for a total of 55 patients (52.4%). Then, the degree of disease severity was mild or moderate (79.0%). Meanwhile, in the non-vaccine group, the majority were male patients (54.1%), with the highest BMI categories of overweight to obesity, with a total of 86 patients (50.6%) and a severe or critical degree of severity (74.7%) (Table 1).

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).

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

Patient characteristics	Remdesivir		Favipiravir	
	Vaccine (n=105)	Non vaccine (n=170)	Vaccine (n=47)	Non vaccine (n=86)
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 Comorbidity	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%)
Body mass index (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	Remdesivir			Favipiravir		
	Vaccine (n=105)	Non vaccine (n=170)	*P*`	Vaccine (n=47)	Non vaccine (n=86)	*P*
Clinical condition improvement						
Improve	94 (89.5%)	91 (53.5%)	0.0001*	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%)	0.0001*	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%)	0.0001*	46 (97.9%)	83 (96.5%)	1.000
Yes	10 (9.5%)	56 (32.9%)		1 (2.1%)	3 (3.5%)	

Note: *significant *P*<0.05

In general, the characteristics of the patients were quite similar for the vaccine and non-vaccine groups. Most of the patients in both groups were female, adult patients with an mean age of 49.33±16.72 had a history of comorbidities, had more than 1 comorbidity with mild/moderate severity, and had an mean 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 of 151 (59.3%) (Table 1).

The assessment of the effectiveness of therapy is based on the clinical condition improvement, length of stay, and mortality of COVID-19 patients. A total of 89.5% of patients who were treated with remdesivir in the vaccine group experienced an improvement in their clinical condition compared to those in the non-vaccine group (OR=0.135; 95% CI=0.067-0.270; *P*=0.0001). 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 59.4% of those in the non-vaccine group had a length of stay 1–14 days (OR=0.244; 95% CI=0.130-0.456; *P*=0.0001) (Table 2).

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*=0.0001). Among 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 this was not statistically significant (OR=0.212; 95% CI=0.026-1.749; *P*=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 the non-vaccine group had a length of stay of <14 days, but it was not statistically significant (OR=0.720; 95% CI=0.134-3.863; *P*=1.000). For the mortality parameter, 97.9% of patients in the vaccine group did not die even though it was not statistically significant (OR=0.601; 95% CI=0.061-5.949; *P*=1.000) (Table 2).

In this study, it was also observed 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 (*P*<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 or critical severity had improved clinical condition (OR=0.147; 95% CI=0.080-0.273; *P*=0.0001). On the length of stay parameter, gender (OR=0.572; 95% CI=0.339-0.966; *P*=0.037) and the degree of COVID-19 severity (OR=0.087; 95% CI=0.042-0.180; *P*=0.0001) were risk factors that significantly affected the length of stay of COVID-19 patients who were given remdesivir therapy with *P*<0.05 (Table 3).

In terms of the mortality parameter, it was obtained that age, comorbidities, and disease severity were risk factors that significantly affected mortality in COVID-19 patients who were given remdesivir therapy (*P*<0.05). About 81.5% of adult patients (OR=2.016; 95% CI=1.152-3.530; *P*=0.015), 100% of patients with no comorbidities, and 88.9% of patients with mild or moderate severity (OR=0.233;

95% CI=0.122-0.447; *P*=0.0001) did not experience mortality.

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

DISCUSSION

This study showed that the patient's vaccination status affected 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%).[24,25]

Table 3. Factors affecting the effectiveness of remdesivir therapy

Risk Factor	Clinical condition improvement			Length of stay			Mortality		
	Improve	Worsen	*P*	1-14 days	>14 days	*P*	No	Yes	*P*
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%)	0.0001*
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%)	0.0001*	116 (92.1%)	10 (7.9%)	0.0001*	112 (88.9%)	14 (11.1%)	0.0001*
Severe/Critical	75 (50.3%)	74 (49.7%)		75 (50.3%)	74 (49.7%)		97 (65.1%)	52 (34.9%)	

Note: *significant *P*<0.05

Table 4. Factors affecting the effectiveness of favipiravir therapy

Risk Factor	Clinical condition improvement			Length of stay			Mortality		
	Improve	Worsen	*P*	1-14 days	>14 days	*P*	No	Yes	*P*
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%)	

Note: *significant *P*<0.05

Meanwhile, patients receiving favipiravir therapy in the vaccine group indicated good clinical condition improvement compared to those in the non-vaccine group (97.9% vs 90.7%) although not statistically significant. This is compatible with previous studies, which obtained that vaccination and antivirals had a synergistic effect, and also that vaccination and administration of remdesivir in high-risk patients could prevent the clinical development of COVID-19 towards a more severe one. [24,25]

Another study found that the use of remdesivir revealed good improvement in clinical conditions.[7] There was also a study that indicated that favipiravir therapy could increase clinical improvement on days 7 and 14, but this was not statistically significant.[9] Remdesivir and favipiravir are RNA-dependent RNA polymerase (RdRP) inhibitors that are predicted to be able to treat severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[3,26] The clinical condition improvement of the patient 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 discovered that the degree of severity affected improvement in clinical conditions, length of stay, and mortality. This is in line with previous studies which stated that severity could affect the patient's recovery process.[27] Generally, the severity of COVID-19 is associated with the systemic inflammation experienced by patients, which can increase the risk of mortality.[28] Patients with mild COVID-19 have better clinical condition improvement, shorter lengths of stay, and a lower risk of mortality. This result is associated with the infection process of 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 act by inhibiting viral RdRp which then reduces viral replication rates.[30] Reduced viral load and a good immune response mean that there is no inflammatory response in the body, which leads to clinical condition improvement. The severity of COVID-19 is associated with an increase in the inflammatory reaction.[4]

The results of this study also noticed that the patient's vaccination status affected the reduction in 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 and 14 days (85.7% vs 59.4%) compared to those in the non-vaccine group (9.5% vs 32.9%) and also had a lower risk of 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 and 14 days (95.7% vs 94.2%) and lower mortality (2.1% vs 3.5%) than those in the non-vaccine group, but this was not statistically significant. [24,25]

This result is consistent with previous studies showing that antiviral treatment combined with vaccination could be a strategic tool that significantly reduced the length of stay and mortality, and it was also pointed out that vaccination plus remdesivir administration reduced hospitalization time, and no intubation or death was reported. [24,25] Besides, other studies revealed that vaccination reduced the length of stay and mortality in COVID-19 patients.[12,13]

This study also observed that vaccination can reduce the severity of disease in COVID-19 patients who had been vaccinated compared to those who had not been vaccinated. This is in line with a study from Muhammed et al., which reported that vaccines reduced the incidence of infection and disease severity.[12]

The main results of this study were that the vaccination had a good effect on the effectiveness of remdesivir and favipiravir therapy in patients with COVID-19, and there was 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 is helping to formulate the treatment.

LIMITATION

As this study was only conducted in one hospital, the results cannot be generalized. However, this study can describe the vaccination effect 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 in more than one location and consider some other variables.

CONCLUSION

It can be concluded that the degree of COVID-19 severity is a risk factor that can affect the effectiveness of COVID-19 antiviral therapy. 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 alternatives to cure COVID-19 patients.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCE

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
2. Handayani D, Hadi DR, Isbaniah F, Burhan E, Agustin H. Penyakit virus corona 2019. J Respir Indones. 2020;40(2):119–29.
3. Alamer A, Alrashed AA, Alfaifi M, Alosaimi B, AlHassar F, Almutairi M, et al. Effectiveness and safety of favipiravir compared to supportive care in moderately to critically ill COVID-19 patients: a retrospective study with propensity score matching sensitivity analysis. Curr Med Res Opin. 2021;37(7):1085–97.
4. Damayanti H, Sajinadiyasa IGK, Risni HW, Sauriasari R. The Effectiveness and Safety of Favipiravir in COVID-19 Hospitalized Patients at Tertiary Referral Hospital, Bali, Indonesia. Kesmas. 2021;16(4):289–97.
5. PDPI, PERKI, PAPDI, PERDATIN, IDAI. Pedoman tatalaksana COVID-19: Edisi 4. Indonesia: 4; 2022.
6. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020;383(19):1813–26.
7. Garibaldi BT, Wang K, Robinson ML, Zeger SL, Bandeen-Roche K, Wang MC, et al. Comparison of Time to Clinical Improvement with vs without Remdesivir Treatment in Hospitalized Patients with COVID-19. JAMA Netw Open. 2021;4(3):1–14.
8. Mozaffari E, Chandak A, Zhang Z, Liang S, Thrun M, Gottlieb RL, et al. Remdesivir treatment in hospitalized patients with COVID-19: a comparative analysis of in-hospital all-cause mortality in a large multi-center observational cohort. Clini Infect Dis. 2021;2019.
9. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020;6(10):1192–8.
10. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir Versus Arbidol for Clinical Recovery Rate in Moderate and Severe Adult COVID-19 Patients: A Prospective, Multicenter, Open-Label, Randomized Controlled Clinical Trial. Front Pharmacol. 2021;12:1–11.

11. Bernal JL, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. The BMJ. 2021;373.
12. Mohammed I, Nauman A, Paul P, Ganesan S, Chen KH, Jalil SMS, et al. The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. Hum Vaccin Immunother. 2022;18(1).
13. Ramakrishnan M, Prakash S, Nagar J. Impact of vaccination in reducing hospital expenses, mortality and mean length of stay among COVID-19 patients – A retrospective cohort study from India. medRxiv. 2021;
14. Soegiarto G, Purnomosari D, Wulandari L, Mahdi A, Fahmita D, Hadmoko T. Articles Incidence of SARS-CoV-2 infection in hospital workers before and after vaccination programme in East Java , Indonesia – A retrospective cohort study. The Lancet Reg Health - Southeast Asia. 2023;10:100130.
15. Cucunawangsih C, Wijaya RS, Lugito NPH, Suriapranata I. Post-vaccination cases of COVID-19 among healthcare workers at Siloam Teaching Hospital, Indonesia. Int J Infect Dis. 2021;107:268–70.
16. BPOM, JICA. Modul farmakovigilans untuk tenaga profesional kesehatan, proyek “ensuring drug and food safety.” Jakarta: Badan Pengawas Obat dan Makanan; 2020.
17. Marshall JC, Murthy S, Diaz J, Adhikari N, Angus DC, Arabi YM, et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20(8):e192–7.
18. Olender SA, Perez KK, Go AS, Balani B, Price-Haywood EG, Shah NS, et al. Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care. Clin Infect Dis. 2021;73(11):E4166–74.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62.
20. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507–13.
21. Hafiz M, Icksan AG, Harlivasari AD, Aulia R, Susanti F, Eldinia L. Clinical, radiological features and outcome of COVID-19 patients in a secondary Hospital in Jakarta, Indonesia. J Infect Dev Ctries. 2020;14(7):750–7.
22. Pranata R, Lim MA, Yonas E, Vania R, Lukito AA, Siswanto BB, et al. Body mass index and outcome in patients with COVID-19: A dose–response meta-analysis. Diabetes Metab. 2021;47(2):101178.
23. Kementerian PPN, Bappenas. Buku studi pembelajaran penanganan COVID-19 Indonesia. Jakarta, Bappenas; 2021.
24. Matrajt L, Brown ER, Cohen MS, Dimitrov D, Janes H. Could widespread use of antiviral treatment curb the COVID-19 pandemic? A modeling study. BMC Infect Dis. 2022;22(1):1–16.
25. Panagopoulos P, Petrakis V, Trypsianis G, Papazoglou D. Early 3-day course of remdesivir in vaccinated outpatients with SARS-CoV-2 infection. A success story. J Chemo. 2022;34(8):550–3.
26. Instiaty, Sri Darmayani IGAAP, Marzuki JE, Angelia F, William, Siane A, et al. Antiviral treatment of covid-19: A clinical pharmacology narrative review. Med J Indones. 2020;29(3):332–45.
27. Tan L, Kang X, Ji X, Li G, Wang Q, Li Y, et al. Validation of Predictors of Disease Severity and Outcomes in COVID-19 Patients: A Descriptive and Retrospective Study. Med. 2020;1(1):128-138.e3.
28. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting disease severity and outcome in COVID-19

patients: A review of multiple biomarkers. Arch Pathol Lab Med. 2020;144(12):1465–74.

29. Goyal A, Cardozo-Ojeda EF, Schiffer JT. Potency and timing of antiviral therapy as determinants of duration of SARS-CoV-2 shedding and intensity of inflammatory response. Sci Adv. 2020;6(47):1–13.
30. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;323(18):1824–36.