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The Effectiveness and Safety of Favipiravir in COVID-19 Hospitalized Patients at Tertiary Referral Hospital, Bali, Indonesia

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Abstract

COVID-19 is a major public health problem, with still questionable specific cure. Favipiravir is a COVID-19 antiviral that is potentially a therapy for COVID-19. This study aimed to analyze its effectivity and safety in moderate to critical hospitalized patients. This study was a retrospective cohort in a tertiary referral hospital in Denpasar City, Bali Province, Indonesia, from August 2020 to January 2021. There was a total of 192 patients; 96 in the favipiravir group and 96 in the non-favipiravir group (remdesivir/oseltamivir). Effectivity was measured by assessing the clinical condition at the end of the isolation period of 14 days. The favipiravir group showed better clinical conditions than the non-favipiravir group (79.2% vs. 56.3%; adjusted RR = 2.196; 95% CI = 1.084 – 4.451; p-value = 0.029), seen from being free of fever and respiratory problems. Stratification analysis demonstrated that the clinical improvement was significantly different in the severe/critical group in favor of favipiravir (RR = 1.573; 95% CI = 1.139-2.172). The most common non-serious adverse events (AE) found in the use of favipiravir were gastrointestinal disturbances (12.5%). In brief, favipiravir is effective in severe/critical cases, and less serious AE were found in its use. Appropriate treatment is expected to help in reducing the public health burden.

Keywords: COVID-19, effectivity, favipiravir, safety

Introduction

As of March 2020, coronavirus disease 2019 (COVID-19) has been declared a global pandemic by World Health Organization (WHO). By October 19, 2021, there have been 240 million cases and 4.9 million deaths.[1] The mortality and morbidity of COVID-19 have been dramatically increasing, making this disease a major global public health burden.[2] Health expenditure was found to be associated with case fatalities,[3] which medication use would be one of the factors that contribute to the increase of health expenditure.[4] Therefore, comprehensive measures need to be taken to solve pandemics effectively and efficiently by ensuring a good quality of health services from preventive to curative actions. Inappropriate treatment is of concern that needs to be addressed to help reduce morbidity and mortality.

To date, substantial researches about COVID-19 treatment are still ongoing. Several potential antivirals have been tested and recommended to treat COVID-19 in several countries, including Indonesia.[5] Favipiravir was first used in Japan to treat influenza and Ebola.[6] It is a prodrug with its active form of favipiravir ribofuranosyl-5′-triphosphate (Favipiravir-RTP) that binds to and inhibits viral RNA-dependent RNA polymerase (RdRp), resulting in inhibition of viral genome transcription and replication.[6,7] In China, a preliminary COVID-19 antiviral trial reported that taking oral favipiravir 1,600 mg twice daily on the first day, followed by 600 mg twice daily, produced better results than oral lopinavir/ritonavir (400 mg/100 mg) twice daily.[8] A study in Thailand showed different results; favipiravir was no more effective for patients with severe COVID-19 compared to lopinavir/ritonavir.[9] In Indonesia, there are still little data regarding the effectiveness of using favipiravir in COVID-19 patients.

Indonesian Medical Association recommends favipiravir as therapy for COVID-19 patients with mild to critical conditions.[10] The National Food and Drug Administration of Indonesia issued an emergency use authorization (EUA) for favipiravir as a drug for patients hospitalized with mild to moderate COVID-19 symptoms.[11] To ensure the quality of drugs, especially for drugs that are still in emergency use, it is necessary to monitor the effectiveness and safety of their therapy.[12] Given the limited data about favipiravir, this study aimed to compare the effectiveness and safety of favipiravir with

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non-favipiravir in moderate to critical COVID-19 patients at a tertiary referral hospital in Denpasar City, Bali Province, Indonesia.

Method

An observational study using retrospective cohort design was conducted at a tertiary referral hospital in Denpasar City, Bali Province, Indonesia. This study was carried out by adapting a previous study by Cai, *et al.,*[8] regarding the evaluation of the effect of favipiravir versus lopinavir/ritonavir in COVID-19 patients. In this study, the effectiveness of therapy was assessed based on the time of viral clearance and improvement of chest CT scan on day 14 after treatment. The Ethics Committee approved the study protocol of the Faculty of Medicine, Udayana University, and Sanglah Hospital (number 78/UN14.2.2.VII.14/LT/2021). Study permission was obtained from the President Director of Sanglah General Hospital, Denpasar City (number LB.02.01/XIV.2.2.1/3023/2021). The Ethics Committee ruled out the need for consent because there is no direct intervention with the patients.

The study population consisted of moderate to critical COVID-19 confirmed patients aged over 18. This study excluded patients who were pregnant/breastfeeding, had a history of hemodialysis or chronic liver disease, had switched antiviral therapy during treatment, and had incomplete medical record data. The sample calculation was calculated based on the formula of a cohort study from Sastroasmoro (Formula 1),[13] and the result of the study from Cai, *et al.,*[8] with a significance level of (α) 5%; power of study (β) 80%; the proportion of improved COVID-19 patients with favipiravir (P_1) therapy was 0.56; and the proportion of improved patients with non-favipiravir (P_2) therapy was 0.35, the minimum samples required was 87 for each group. The amount of sample added 10% to avoid drop out. The selection of the subjects was made using total sampling until the number of required subjects was met.

Data were taken from medical records and databases covering the period of August 2020 to January 2021 since favipiravir was first used as a COVID-19 therapy at a tertiary referral hospital in Denpasar City, Bali Province, Indonesia. The patient data collected included demographic, comorbidities, history of antiviral therapy (the type of antiviral that had been given and time of antiviral administration), unexpected events encountered while receiving antiviral therapy, and the clinical outcomes (the patient's condition on the last day of isolation, x-ray, and polymerase chain reaction (PCR) test results).

$$n = \frac{\{Z_{1-\alpha/2}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{p1(1-p1)+P_2(1-P_2)}\}^2}{(p1-p2)^2}$$

Notes: n: Number of Samples, Z_α: Level of Significance, Z_β: Power, P_1: Proportion of Effects in the Risk Group, P_2: Proportion of Effects in the Non-Risk Group Estimated Proportion, Q = 1-P.

Formula 1. Estimated Sample Size for Cohort Study with Hypothesis Testing on Relative Risk

In this study, pre- and post-treatment analyses were not assessed. Comparison was made by assessing the favipiravir and non-favipiravir groups based on patients' conditions on their last day of isolation. The therapeutic efficacy was assessed from the improvement in clinical conditions at the end of the isolation period, characterized by no longer showing fever symptoms and respiratory problems (cough, shortness of breath, and rapid breathing) for moderate and severe or critical symptoms patients.[10] The assessment of this condition was based on the physician's judgment, which was recorded in the medical record. Additional follow-up of chest X-ray and PCR test results were only performed in patients with severe or critical symptoms.[10] The endpoint of observation was on the last day of the isolation period, which was the 14th day calculated from the first time the patient showed symptoms of COVID-19.[10] The Centers for Disease Control and Prevention (CDC) also recommends isolation for at least ten days after symptom onset and three days after symptom improvement.[14] The safety of the therapy was assessed by observing adverse events (AE) that happened to patients after treatment of favipiravir.

This study categorized sex as male and female. Male and female have physiological differences with the presence of female's hormone (estrogen and progesterone) was associated with better immunity.[15] Age was categorized by group according to WHO.[16] The study subjects were adult patients (>18 years) and the elderly group (≥60 years), which were age groups that were at risk of being infected and getting worsening conditions due to COVID-19.[17] The body mass index (BMI) category was based on the national BMI classification from the Indonesian Ministry of Health,[18] which was divided into thin (<18.5), normal (18.5 – 25.0), and obese (>25). The obese BMI group was associated with the risk of infection and worsening of the COVID-19 condition.[19] Severity category was based on the COVID-19 management guidelines 2nd edition, namely mild, moderate, and severe/critical.[10]

The severe and critical were included in one group, namely patients in severe condition. Comorbidities were divided into Yes and No because several studies,[17,20-22] have shown comorbidity is associated with the severity and mortality of COVID-19 patients.[23] Time of administration of antivirals is associated with the process of clearing the virus in the body and the effectiveness of therapy.[24] A study from Lauer, *et al.,*[25] stated that the average incubation period for COVID-19 is five days.

Administration of antivirals within six days of symptom onset can reduce viral load and the risk of adverse inflammation-related infections.[24] All of the covariates were suspected as confounding variables for the clinical improvement

All data were analyzed using IBM SPSS statistic base software, version 22. Descriptive analysis was used to describe the demographic and clinical information of the patients. Categorical data were displayed in the form of proportions (%) and numerical data in the form of Mean±SD if the data were normally distributed, or median (min-max) if not normally distributed. Bivariate analysis was used to analyze the effect of antiviral therapy or those confounding variables on clinical improvement. Categorical data were analyzed using the Chi-square test or Fisher's Exact Test. Factors that had p-value<0.25 on the bivariate test were further analyzed using multivariate logistic regression analysis, reported as the adjusted risk ratio (aRR) with a 95% confidence interval (CI). The multivariate analysis took out variables that had p-value > 0.05 from the multivariate model one by one started with the biggest p-value. If the RR of remaining variables changed >10%, the excluded variables were back to the model and considered confounding variables. Stratification analysis was done to observe further the effect of confounding variables on clinical improvement. The safety of the therapy was analyzed descriptively in terms of proportion (%). Observed unexpected events were then analyzed using the Naranjo scale to assess causality and the degree of adverse events

Results

A total of 192 medical records of patients were evaluated. Each favipiravir and the non-favipiravir group consisted of 96 patients that met the criteria. The patient characteristics were generally the same for both groups (Table 1). Most of the patients were male, adult, and had normal BMI. Most had a history of comorbidities, the

Table 1. Patient Characteristics during COVID-19 Therapy at a Tertiary Referral Hospital in Denpasar City, Bali, Indonesia

Patient Characteristic	Category	Antiviral Therapy	
		Favipiravir (n = 96)	Non-favipiravir (n = 96)
		n (%)	n (%)
Gender	Female	36 (37.5)	35 (36.5)
	Male	60 (62.5)	61 (63.5)
Age, years	Mean±SD	51.5±12.9	56.2±12.2
	Adult (18-59)	71 (74)	60 (62.5)
	Elderly (60)	25 (26)	36 (37.5)
Body mass index (kg/m²)	Mean±SD	23.9±3.5	24.3±3.2
	Thin–normal (25)	63 (65.6)	62 (64.6)
	Overweight (>25)	33 (34.4)	34 (35.4)
Degree of severity	Moderate	46 (47.9)	22 (22.9)
	Severe	50 (52.1)	74 (77.1)
Comorbidity history	No	41 (42.7)	33 (34.4)
	Yes	55 (57.3)	63 (65.6)
Number of comorbid diseases	None	41 (42.7)	33 (34.4)
	One	38 (39.6)	38 (39.6)
	More than one	17 (17.7)	25 (26.0)
Comorbid type	Hypertension (HT)	13 (13.54)	13 (13.54)
	Diabetes mellitus (DM)	10 (10.42)	11 (11.46)
	Cardiovascular disease (CVD)	6 (6.25)	4 (4.17)
	Asthma	4 (4.17)	2 (2.08)
	Tuberculosis (TB)	2 (2.08)	0
	Malignancy	0	4 (4.17)
	Immune disorders	1 (1.04)	3 (3.13)
	Hematological disorders	1 (1.04)	0
	Gastrointestinal disorders	0	1 (1.04)
	Gout	1 (1.04)	0
	DM+HT	4 (4.17)	6 (6.25)
	DM+CVD	2 (2.08)	5 (5.21)
	HT+CVD	2 (2.08)	3 (3.13)
	DM+HT+CVD	3 (3.13)	1 (1.04)
	Other combinations*	6 (6.25)	10 (10.25)
D-day administration of antiviral**	Mean±SD	6.3±3.10	6.9±3.6
	≤5	48 (50)	38 (39.6)
	>5	48 (50)	58 (60.4)

Notes: SD = Standard Deviation, *Other combinations = more than one comorbidity other than combination mentioned above, **D-day administration of antiviral starting from the onset of the symptom.

most common being hypertension. The favipiravir group comprised an equal amount of moderate and severe/critical patients, while non-favipiravir was dominated by severe/critical patients. On average, patients in both groups received their first antiviral on day six after the first sign of symptoms.

A total of 79% of patients in the favipiravir group experienced an improvement in their clinical condition, which was free from fever and respiratory problems by the end of the isolation period compared to the non-favipiravir group (RR = 1,407; 95% CI = 1.148-1.726; p-value = 0.001) (Table 2).

Age, disease severity, and history of comorbidities were variables that significantly affect the improvement of a patient's clinical condition by the end of the isolation period. However, multivariate analysis showed that comorbidity history and severity of COVID-19 had a statistically significant effect on improving clinical conditions. In the final model, antiviral therapy, together with comorbidity history and severity, significantly affected clinical improvement (Table 3). The result of the stratification analysis of the degree of severity is shown in Table 4. In the moderate group, clinical improvement was not significantly different, while in the severe group was significantly different.

Adverse events (AE) due to favipiravir use were observed in 21 individuals (21.9%) and the case of non-favipiravir treatment in 25 individuals (26%). The most common adverse events found with the use of favipiravir were gastrointestinal disturbances (12.5%), while with

Table 2. Factors that Influence the Improvement of Clinical Condition of COVID-19 Patients

Risk Factor	Category	Improvement in Clinical Condition[a]		p-value	RR (95% CI)
		Stable/Worse	Improved		
		n (%)	n (%)		
Antiviral	Non-favipiravir	42 (43.8)	54 (56.3)	0.001	1.407 (1.148–1.726)
	Favipiravir	20 (20.8)	76 (79.2)		Ref
Gender	Male	40 (33.1)	81 (66.9)	0.767	1.031 (0.844–1.259)
	Female	22 (31)	49 (69)		Ref
Age	Elderly (60)	26 (42.6)	35 (57.4)	0.037*	1.264 (0.994–1.6080
	Adult (18-59)	36 (27.5)	95 (72.5)		Ref
Body mass index	Overweight	19 (28.4)	48 (71.6)	0.393	0.916 (0.752–1.115)
	Thin-normal	43 (34.4)	82 (65.6)		Ref
Degree of severity	Severe	58 (46.8)	66 (53.2)	<0.001*	1.768 (1.484–2.107)
	Moderate	4 (5.9)	64 (94.1)		Ref
Comorbidity history	Yes	46 (39)	72 (61)	0.012*	1.285 (1.065–1.549)
	No	16 (21.6)	58 (78.4)		Ref
D-day administration of antiviral	>5	37 (34.6)	69 (65.1)	0.390	1.090 (0.897–1.323)
	≤5	25 (29.1)	61 (70.9)		Ref

Notes: RR = Risk Ratio, CI = Confidence Interval, [a]Reference: improved

Table 3. Logistic Regression Analysis for the Improvement of Clinical Condition of COVID-19 Patients

Model	Confounding Variable	Category	p-value	RR	95% CI
Crude	Antiviral	Non-favipiravir	0.001*	1.407	1.148–1.726
		Favipiravir		Ref	
Adjusted	Antiviral	Non-favipiravir	0.047*	2.066	1.011–4.222
		Favipiravir		Ref	
	Age	Elderly	0.090	1.888	0.905–3.939
		Adult		Ref	
	Degree of severity	Severe	0.000*	12.898	4.305–38.638
		Moderate		Ref	
	Comorbidity history	Yes	0.027*	2.320	1.099–4.898
		No		Ref	
Adjusted	Antiviral	Non-favipiravir	0.029*	2.196	1.084–4.451
		Favipiravir		Ref	
	Degree of severity	Severe	0.000*	12.442	4.189–36.960
		Moderate		Ref	
	Comorbidity history	Yes	0.022*	2.377	1.134–4.985
		No		Ref	

Notes: RR = Risk Ratio, CI = Confidence Interval

Table 4. Stratification of Degree of Severity on Improving the Clinical Condition of COVID-19 Patients

Category	Antiviral	Clinical Improvement[a]		p-value	RR (95% CI)
		Stable/Worsened	Improved		
		n (%)	n (%)		
Moderate	Non-favipiravir	0 (0)	22 (100)		0.913 (0.835-0.998)
	Favipiravir	4 (8.7)	42 (91.3)	0.296	Ref
Severe	Non-favipiravir	42 (56.8)	32 (43.2)		1.573 (1.139-2.172)
	Favipiravir	16 (32)	34 (68)	0.010*	Ref

Notes: RR = Risk Ratio, CI = Confidence Interval, [a]Reference: improved

Table 5. The Proportion of Adverse Events in COVID-19 Patients

Adverse Event	Antiviral Therapy	
	Favipiravir (n = 96)	Non-favipiravir (n = 96)
	n (%)	n (%)
Less Serious Adverse Event:		
Indigestion	12 (12.5)	6 (6.25)
Nauseous vomiting	2 (2.08)	1 (1.04)
Constipation	6 (6.25)	2 (2.08)
Bloating	4 (4.17)	1 (1.04)
Diarrhea	0	2 (2.08)
Heartburn	1 (1.04)	0
Numbness on cheeks and lips	1 (1.04)	0
Increased liver enzymes	5 (5.21)	14 (14.58)
SGOT upgrade	4 (4.17)	4 (4.17)
SGPT increase	1 (2.08)	10 (10.42)
Combination	2 (2.08)	4 (4.17)
Constipation and increase in SGPT	1 (1.04)	1 (1.04)
Constipation and increased SGOT	0	1 (1.04)
Nauseous vomiting and increased SGOT	0	1 (1.04)
Diarrhea and increased SGPT	1 (1.04)	0
Heartburn and constipation	0	1 (1.04)
Serious Adverse Event		
Death	2 (2.08)	15 (15.62)

Notes: SGOT = Serum Glutamic Oxaloacetic Transaminase, SGPT = Serum Glutamic Pyruvic Transaminase

non-favipiravir, elevated liver enzymes (15.3%) were most prevalent (Table 5). The Naranjo scale's causality analysis showed that all the observed adverse events were categorized as "possible." The possible category means that the AE may possibly be affected by favipiravir.

Discussion

COVID-19 has been a global pandemic that needs a prompt response from stakeholders, including study institutions and health facilities. The increasing cases in Indonesia have become one of the reasons for the government to prioritize health sectors. One of the efforts that must be done is ensuring the availability of quality and safe health services.[26] The critical challenge for most countries to pandemic includes the rapid formulation of treatment guidelines and their dissemination to health stakeholders and communities so morbidity and mortality can be suppressed.[27] This study has analyzed the promising potential of favipiravir as a moderate to critical COVID-19 antiviral, as has been previously reported in other countries such as China,[8], India,[28], Iran,[29] and Thailand.[9] In this study, stable and worse conditions were classified as one condition because stable means no clinical improvement, which indicated that the drug was not effective.

This study showed that favipiravir could increase the chance of improvement in the clinical condition of COVID-19 patients by the end of their isolation period compared to non-favipiravir antivirals (79.2% vs. 56.3%; RR = 2.196; 95% CI = 1.084-4.451; p-value = 0.029). This clinical improvement was mainly characterized by free from fever and respiratory problems at the end of the isolation period of 14 days. This condition is in line with the study of Cai, *et al.,*[8] who showed that favipiravir therapy was able to increase clinical improvement on the 7th and 14th day, but statistically not signif-

icantly. The meta-analysis study reported significant clinical improvement on the favipiravir group on the 7th and 14th day of treatment (Day 7: RR = 1.25, 95% CI = 1.01-1.53; Day 14: RR = 1.29, 95% CI = 1.08-1.54).[30] In the non-favipiravir group, patients received either oseltamivir or remdesivir. A study in China, which used oseltamivir at the beginning of the COVID-19 pandemic, suggested that administering oseltamivir may reduce the risk of death in COVID-19 patients.[31] Oseltamivir is an effective neuraminidase inhibitor drug for treating influenza.[32] However, neuraminidase was not found in the SARS-CoV-2 virus, so how oseltamivir is not thought to be effective enough to treat COVID-19,[32] was in line with the result of this study. Remdesivir is an antiviral that acts by inhibiting RdRp on synthesis and replication of viral RNA,[33] which is thought to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, the result of this study showed that patients who received remdesivir had no better clinical condition than favipiravir. This result was in line with the solidarity trial from WHO that state remdesivir have little or no effect on hospitalized COVID-19, as indicated by overall mortality.[34]

The study showed that the factors of age, severity, and history of comorbidities might affect the improvement of clinical conditions.[17,20,22] However, this study revealed that only the degree of severity and history of comorbidity were the significant factor influencing improvement in patients' conditions by multivariate analysis. In this study, 57.3% of patients in the favipiravir group had a history of comorbidities (vs. 65.6% in the non-favipiravir group). The most common comorbidities were hypertension and diabetes mellitus. This is in line with the study by Zaki, *et al.*,[20] stating that diabetes and hypertension are correlated with the severity of COVID-19. Hypertension and COVID-19 are related to angiotensin-converting enzyme (ACE2), which is suspected to be the portal of entry SARS-CoV-2.[22] Binding of SARS-CoV-2 virus to ACE2 can reduce the physiological function of ACE2 then lead to a potential mechanism for severity symptoms and multi-organ dysfunction, that can be seen in severe COVID-19 infection.[35] There are several possible mechanisms that can increase the risk of patients of diabetes mellitus to COVID-19 infection, such as immunological dysregulation, increased susceptibility to hyper-inflammation, and cytokine storm syndrome.[21] Poor glycemic control can cause a delay in the activation of T cells and NK cells which causes the delay in responding to viral infection.[21,36] Hyperglycemia also increases proinflammatory cytokines (e.g., Interleukin 6 (IL-6)), which causes a cytokine storm so that people with diabetes are susceptible to severe COVID-19 infection.[36]

Severity may affect the patients' recovery process.[37] This study demonstrated that clinical improvement was more apparent in moderate cases regardless of which antiviruses were given. Patients with severe symptoms generally have systemic inflammation that can increase the risk of death.[38] Those with milder COVID-19 is more likely to experience clinical improvement. These results may be related to the mechanism of the pathogenesis of the SARS-CoV-2 virus. At a lower level, the virus is still in the replication phase, so the antiviral is more effective in preventing its spread.[24] Favipiravir works by inhibiting the RdRp of the virus,[6] which may reduce the number of viral replications.[7] The reduced number of viruses and a good immune response mean that the body does not have an inflammatory reaction, leading to clinical improvement. The more severe the degree of COVID-19, the greater the possibility of an increased inflammatory reaction. In this phase, the improvement of the condition may be influenced more by immune response-suppressing drugs (such as steroids) than by antiviral therapy.[24] However, this study found that after stratification analysis, favipiravir in severe cases showed significantly improved clinical condition compared to non-favipiravir. This happened probably because of the anti-inflammatory effect of favipiravir.[39] The respiratory distress of SARS-CoV-2 is thought not only direct viral action but also to chemical mediators induced by SARS-CoV-2. Favipiravir could partially control the inflammatory mediators.[39]

Adverse events (AE) were found in both the favipiravir and non-favipiravir antiviral groups (21.9% favipiravir, 26% non-favipiravir). In the favipiravir group, the most common AE was gastrointestinal disturbances (12.5%), followed by increased liver enzymes (5.21%), and numbness in the cheeks and lips (1.04%). This finding is in line with previous studies, which have found that favipiravir causes elevated liver enzymes (to a mild to a moderate degree), increased total bilirubin, increased uric acid, and gastrointestinal disturbances.[40,41] The most common AE in the non-favipiravir group was an increase in liver enzymes (14.6%). The use of remdesivir sometimes causes an increase in SGOT or SGPT grade 1 or 2 but is still within tolerable limits.[42] During the treatment process, none of the patients had their antiviral treatment discontinued due to AE. Looking at these results, AEs tend to be equal in both groups (favipiravir and non-favipiravir) with a tolerable effect.

Adverse drug reactions causality analysis using the Naranjo algorithm shows that the average causality score is 4 (possible category), which means that the adverse events were possibly related to favipiravir. This result indicated that other factors should also be considered as the cause of adverse effects, for example, the mechanism of the COVID-19 disease. The ACE2 receptor, the entry site for SARS-CoV-2, is also present in the digestive tract, thus allowing intestinal disturbances to occur due to viral infection.[43] Digestive symptoms commonly encountered

in COVID-19 patients are anorexia, nausea and/or vomiting, diarrhea, and abdominal pain.[44] In severe COVID-19 patients, serum aminotransferases may be elevated (<5x upper normal limit).[44] SARS-CoV-2 has the potential to cause liver dysfunction and liver enzyme abnormalities. Hyperinflammation due to cytokine storm is also a cause of liver damage due to COVID-19 infection.[45] Other concomitant drugs may also contribute to the adverse effects of patients since nausea, vomiting, and other effects were also common in many drugs. Further study is needed to confirm the finding by challenging and rechallenging the antivirals to the patients.

The main finding of this study is that favipiravir is promising for COVID-19 treatment, especially for severe cases. This study gives evidence to help in formulating treatment guidelines, especially in Indonesian populations, in the hope of reducing the public health burden. In terms of price, remdesivir is the most expensive antivirus at IDR 510,000 per vial. While oseltamivir is IDR 26,000/capsule and IDR 22,500/tablet for favipiravir. Formal cost-effectiveness analysis is needed, but judging from the price and availability in health facilities (tablets are easier to obtain), the use of favipiravir tends to be more promising for therapeutic effectiveness and cost. Investing in the development of treatments and evaluating their cost-effectiveness should be the focus to inform resource allocation decisions, particularly in low- and middle-income countries.[46] Countries are trying to reduce spending that disrupts economic and social stability, so evaluating cost-effectiveness, especially in COVID-19 antiviral therapy, is one strategy to manage human and economic losses caused by the pandemic.

In this retrospective study method, several important parameters, such as radiological results; PCR CT values; and uric acid levels, which hyperuricemia is the most common side effect of favipiravir, were not observed. Since it is a single-center study, the results cannot be generalized. However, this study provided an overview of the effectiveness and safety of favipiravir in the population of COVID-19 patients in Denpasar City, Bali Province, Indonesia. In addition, the duration of antiviral administration and supportive therapy received by patients were not included as confounding variables in the study. However, patients were taken from the same location according to the same therapeutic guidelines, so the treatment options were relatively similar. Further research could be conducted prospectively in more than one location with several other variables considered.

Conclusion

In conclusion, this study found that favipiravir has promising effectivity for treating COVID-19, especially in severe/critical patients. Favipiravir tends to be safe with less serious AE observed. Favipiravir can be one of the rationales and appropriate treatments choice to cure patients. It is expected that appropriate treatments will help to reduce the public health burden.

Abbreviations

COVID-19: coronavirus disease 2019; WHO: World Health Organization; Favipiravir-RTP: Favipiravir Ribofuranosyl-5′-Triphosphate; RdRp: RNA-dependent RNA Polymerase; ADR: Adverse Drug Reaction; EUA: Emergency Use Authorization; PCR: Polymerase Chain Reaction; CDC: The Centers for Disease Control and Prevention; AE: Adverse Event; BMI: Body Mass Index; SD: Standard Deviation; aRR: Adjusted Risk Ratio; CI: Confidence Interval; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; HT: Hypertension; RR: Relative Risk; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase, SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus 2; ACE2: Angiotensin-Converting Enzyme 2; IL-6: Interleukin 6.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Udayana University, and Sanglah Hospital (number 78/UN14.2.2.VII.14/LT/2021). The Ethics Committee ruled out the need for consent because there is no direct intervention with the patients.

Competing Interest

The authors declare that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Authors' Contribution

HD, RS, and GS conceived and designed the study. HD collected, analyzed, and interpreted the data. HD, RS, GS, and HW wrote the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

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