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The Evaluation of Favipiravir Utilization and Clinical Outcome of Inpatients Covid-19 in Secondary Care Hospital, Central Java

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ABSTRACT

Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is often treated with antiviral drugs such as favipiravir. The efficacy of favipiravir, remains contentious with limited study, especially in the context of Indonesia. This study aimed to determine the impact of favipiravir on COVID-19 patients. It utilized a retrospective data collection methodology and an observational study framework. Data were collected from the medical reports of confirmed COVID-19 patients treated between March 2020 and June 2021 at the Secondary Care Hospital in Banyumas Regency, Central Java Province, Indonesia. The effectiveness of favipiravir was assessed by comparing clinical symptoms before and after its use, focusing on changes in temperature, respiratory rate, and cough symptoms parameters were used to evaluate the effects of using favipiravir on clinical symptoms. The study involved 250 patients that met the inclusion criteria: 90 exhibited mild illness severity, 101 had moderate severity, and 59 presented with severe symptoms. Most reported symptoms included coughing, shortness of breath, weakness, fever, and nausea. The majority of favipiravir patients (n=200; 80%) initiated with a dose of 1600 mg/12 hours, followed by a dose of 600 mg/12 hours, with the most common duration of therapy ranging from 8-14 days (n=145; 58%). Statistical analysis revealed significant improvement in cough, fever, and respiratory rate across all levels disease severity after favipiravir treatment (p=0.0001). In conclusion, favipiravir may positively affect COVID-19 patients across all severity level of illness.

Keywords: COVID-19, favipiravir, clinical outcomes, utilization, antiviral treatment

INTRODUCTION

COVID-19 is an infectious disease caused by a new strain of coronavirus, known as SARS-CoV-2, which first identified in Wuhan, China, in December 2019. This virus has rapidly spread throughout China and beyond, reaching over 216 countries. As of June 16, 2022, there have been a total of 538.506.000 confirmed cases worldwide, along with 6.321.394 reported deaths. Indonesia has the 15thhighest number of confirmed COVID-19 cases globally, totaling 6.065.644, including 156.685 fatalities (World Health Organization, 2022). Additionally, data from the Banyumas Regency Public Health Center reveals a significant incidence of COVID-19 in Banyumas Regency, with 627.888 cases and 33.202 deaths.

COVID-19 symptoms range broadly from mild to severe, often involving fever, cough, shortness of breath, muscular pains, change in taste, loss of smell (anosmia), gastrointestinal disorders, and headaches. In individuals with pre-existing health conditions and the elderly, the disease can be pose a serious, even fatal. According to the World Health Organization (WHO), older people or those with underlying medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease, or cancer are at higher risk of serious illness. Severe symptoms, such as difficulty breathing, loss of speech, and chest pain, which are indicative of conditions like respiratory failure, arrhythmias, and shock, can lead to seriously ill or death in individuals of any age. A person's health

can deteriorate swiftly, potentially resulting in conditions like acute respiratory distress syndrome (ARDS) and sepsis within just a week (Alamer *et al*., 2021).

There is currently no specific antiviral treatment available for COVID-19. Even with the advent of a COVID-19 vaccine, the primary focus of clinical research remains the identification of effective treatment strategies. Therefore, it is important to discover effective antiviral medications to combat the disease and to investigate the therapeutic effects of antiviral drugs. Investigating existing antiviral medications that have proven useful in treating other similar viral infections becomes an efficient strategy for identifying effective drugs. SARS-CoV-2 shares 75-80% of its genomic sequence with SARS-CoV. Several medications, such as ribavirin, interferon, lopinavir/ritonavir, and favipiravir have been utilized in the treatment of SARS or MERS patients (Cai *et al.*, 2020).

The Food and Drug Supervisory Agency has approved favipiravir, one of the most commonly used antiviral drugs in Indonesia, and The Emergency Use Authorization (EUA) permit for the treatment of COVID-19. Favipiravir is a broad-spectrum antiviral RNA synthesis inhibitor that works by specifically inhibiting RNA polymerase, an enzyme crucial for viral RNA synthesis. By inhibiting this process, favipiravir reduces viral transcription and replication (Furuta, Komeno & Nakamura, 2017a). In Japan, favipiravir has been licensed for treating influenza and has demonstrated effectiveness against various strains, including A, B, and C strains (Jordan, Stevens & Deval, 2018). Since SARS-CoV-2 is an RNA virus, its replication and transcription, like other RNA viruses, rely on RNA polymerase. Therefore, the RNA polymerase of SARS-CoV-2 becomes a potential target for favipiravir (Buonaguro *et al*., 2020).

Limited research has been conducted in In Indonesia regarding the effectiveness of favipiravir in treating COVID-19 patients. One Randomized Controlled Trial (RCT) study indicated that favipiravir was ineffective compared to placebo Bosaeed *et al.* (2021). However, another study demonstrated that the group receiving favipiravir showed better clinical improvement than those receiving supportive treatment alone (Udwadia *et al*., 2020). These conflicting findings highlight the controversy surrounding the efficacy of favipiravir, emphasizing the need for further research on its effectiveness for COVID-19. Many studies investigating the efficiency of favipiravir involve experimental methods, which can be costly and challenging to carry out. Despite this, favipiravir is among the medications commonly used in hospitals for treating COVID-19 patients. Therefore, the objective of this study is to evaluate the utilization and clinical outcomes of favipiravir therapy in hospitalized COVID-19 patients.

MATERIALS AND METHODS

Ethics Statement

This research has received approval from The Research Ethics Committee of The Faculty of Health Science, Jenderal Soedirman University, with letter number 325/EC/KEPK/III/2021, as well as approval from The Ethics Committee of The Hospital, with letter number 070.1/194/OL/III/2021.

Subjects

The study included all COVID-19 patients who received treatment at two secondary care hospitals in Banyumas Regency, Central Java Province, Indonesia, between September 2020 and June 2021. The total sampling method was used to select patients who met the inclusion criteria, which consisted of confirmed COVID-19 patients, patients aged 18 years or older who received favipiravir therapy for at least 7 days, and patients with complete medical records containing patient number, gender, age, primary and secondary diagnoses, symptoms, PCR swab results, vital sign tests, and therapy details. Exclusion criteria encompassed negative PCR swab findings, patients under 18 years of age, those who did not receive favipiravir medication, favipiravir therapy for less than 7 days, incomplete medical records, and pregnant women.

Instrument

The Case Report Form (CRF) was employed in this study, containing fields for the medical record number, patient identification (name, gender, age >18 years, height, and weight), treatment date, diagnosis, Polymerase chain reaction (PCR) or Rapid swab test results, respiratory rate (RR), temperature, cough symptoms, and therapy details. Clinical outcomes were assessed based on the improvement of fever, cough, and shortness of breath/hard breathing symptoms documented in the medical records. Additional data regarding symptom improvement included body temperature for fever and respiratory rate for shortness of breath.

According to Guidelines of COVID-19 Management 3th Edition, released by Indonesian Medical Association in December 2020, illness severity was categorized into three levels: mild, moderate, and severe. Mild level was defined as patients exhibiting symptoms of fever, cough, and shortness of breath without viral pneumonia evidence or hypoxia. Moderate level included patients with pneumonia symptoms such as fever, cough, fast breathing/hard breathing, without clinically severe pneumonia. Severe level encompassed patients with pneumonia symptoms such as fever, cough, fast/hard breathing, along with clinically severe pneumonia indicated by a respiratory rate exceeding 30 breaths per minute. The efficacy of favipiravir on COVID-19 patients was evaluated by comparing clinical symptoms, specifically temperature, respiratory rate, and cough, before and after 7 days of treatment**.**

Method and analysis

This research used a cohort study design, collecting retrospective data by accessing patient information from CRF. The data were analyzed using univariate analysis, by calculating percentages and quantities of patient demographic parameters such as gender, age range, subjective data and clinical status, favipiravir administration method, and duration of favipiravir therapy. The effect of favipiravir treatment on clinical outcomes was assessed through bivariate analysis, evaluating clinical symptoms (temperature, respiration rate, cough) before and after favipiravir therapy. Paired T-Test was performed to identify differences in subjective data and clinical status before and after therapy. Wilcoxon test was used for ratio scale data, such as temperature and respiratory rate, while the sign test was used for nominal scale data, such as cough symptoms, if the data were not normally distributed. A significance level of $p<0,05$ was defined to indicate a significant improvement in clinical symptoms COVID-19 patients due to favipiravir treatment.

RESULTS AND DISCUSSION

Characteristic of Patients

A total of 618 medical records were initially obtained, but 368 were excluded due to various reasons, such as negative PCR swab findings, confirmed COVID-19 patients under 18 years of age, patients who did not receive favipiravir medication, patients who got favipiravir therapy for less than 7 days, incomplete medical records, and pregnant women. Consequently, 250 medical records of patients meeting the inclusion criteria were analysed. These were classified based on disease severity into mild (n=90; 37.87%), moderate (n=101; 39.34%), and severe (n=59; 22.79%). The sample comprised mostly male patients (n=126; 50.40%), primaril with moderate severity. The most representated age group was 46-55 years (n=66; 26.4%). A majority of the COVID-19 inpatients at secodary care hospitals in Banyumas Regency (n=136; 54,4%) had comorbidities such as hypertension (n=30; 22.06%) and diabetes mellitus (n=30; 22.06%) (Table I).

This study found that 79.6% (n=199) of COVID-19 patients had abnormal chest X-rays, compared to 14% (n=35) who had normal results, and 6,4% (n=16) for whom the results unknown. Among those with abnormal X-rays, nonspecific pneumonia was the most common finding in confirmed COVID-19 patients (n=148; 74.37%), followed by bronchopneumonia (n=41; 20,60%), and bronchitis (n=10; 5,02%) (Table II). The majority of COVID-19 patients have clinical symptoms including coughing, shortness of breath, weakness, fever, and nausea. Only a small proportion of patients reported myalgia, chest pain, and loss of taste. Other symptoms reported by many patients included headaches, decreased appetite, stomach pain, sore throat, diarrhea, anosmia, and a nasal congestion (Figure 1).

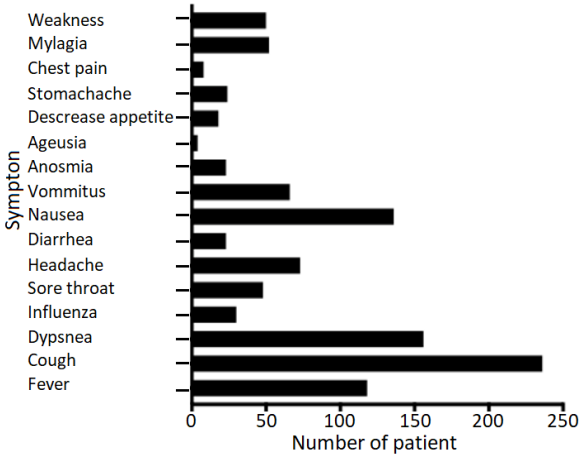

Figure 1. Clinical manifestation of favipiravir in hospitalized COVID-19 patient

Table I. Characteristics of COVID-19 patients

Characteristics		Severity			Total (n=250) (100%)
		Mild (n=90) (37.87%)	Moderate (n=101) (39.34%)	Severe (n=59) (22.79%)	
Gender	Male	44 (48.89%)	53 (52.48%)	29 (49.15%)	126 (50.4%)
	Female	46 (51.11%)	48 (47.52%)	30 (50.85%)	124 (49.6%)
Age (years)	18-25	7 (7.77%)	2 (1.98%)	(1.70%)	10 (4%)
	26-35	14 (15.55%)	7 (6.93%)	5 (8.47%)	26 (10.4%)
	36-45	16 (17.78%)	24 (23.76%)	10 (16.95%)	50 (20%)
	46-55	24 (26.67%)	31 (30.70%)	11 (18.64%)	66 (26.4%)
	56-65	14 (15.56%)	25 (24.75%)	19 (32.20%)	58 (23.2%)
	> 65	15 (16.67%)	12 (11.88%)	13 (22.03%)	40 (16%)
Means of length of stay /LoS (days)		11.68 ± 8.64	12.30±9.60	18.33±11.43	
Comorbidity	**Yes**	38 (27.94%)	56 (41.17%)	42 (30.88%)	136 (54.4%)
	Hypertension	12 (31.58%)	13 (23.21%)	5 (11.90%)	30 (22.06%)
	Diabetes mellitus	8 (21.05%)	13 (23.21%)	9 (21.43%)	30 (22.06%)
	Chronic Heart Failure	1 (2.63%)	8 (14.28%)	7 (16.67%)	16 (11.76%)
	HT + DM	9 (23.68%)	4 (7.14%)	0 (0%)	13 (9.56%)
	Others	8 (21.05%)	22 (39.28%)	21 (50%)	51 (37.5%)
	No	52 (45.61%)	45 (39.47%)	17 (14.91%)	114 (45.6%)

Table II. Thoracic examination in COVID-19 patients

Profile of Chest X-ray	Severity			Total (n=250)
	Mild (n=90)	Moderate (n=101)	Severe (n=59)	
Normal	29 (32.22%)	6 (5.94%)	0 (0%)	35 (14%)
Abnormal	53 (58.89%)	87 (86.14%)	59 (100%)	199 (79.6%)
Unknown	8 (8.89%)	8 (7.92%)	0 (0%)	16 (6.4%)
Abnormal findings				
Bronchitis	7 (13.21%)	3 (3.45%)	0 (0%)	10 (5.02%)
Unspecific pneumonia	35 (66.04%)	63 (73.41%)	50 (84.75%)	148 (74.37%)
Bronchopneumonia	11 (12.22%)	21 (24.14%)	9 (15.25%)	41 (20.60%)

Profile of favipiravir use in COVID-19 patients

Treatment strategies for COVID-19 in the Banyumas Regency Hospital follow the Clinical Management of COVID-19 in Health Service Facilities, as provided by the Minister of Health of the Republic of Indonesia. Favipiravir was introduced inti this treatment in October 2020, following the Emergency Use Authorization (EUA) granted for the drug on September 3, 2020. Consequently, favipiravir usage was minimal in October but peaked in December 2020, correlating with a rise in COVID-19 cases in Central Java during that period, as evidenced by the government's COVID-19 distribution map. Favipiravir, in these hospitals, is administered either alone or in combination with other antivirals for treating mild to severe COVID-19 patients. The typical dosage protocol is an initial loading dose 1600mg/12h, followed by 2x600mg per day for 5 days.

The Indonesian Medical Association recommended three distinct pharmacological therapies for COVID-19, tailored to the severity of the disease: mild, moderate, and severe. Patients with mild symptoms were prescribed multivitamins (B, C, D, E), zinc, azithromycin 1x500mg/day for five days, antivirals (favipiravir or oseltamivir), symptomatic medication (paracetamol for fever, ondansetron for nausea/vomiting, ranitidine/omeprazole), and medications for existing comorbidities. Moderate level patients receive similar treatment but with a course of azithromycin (1x500mg/days) or levofloxacin (750mg/day) extended to 5-7 days, and antivirals including favipiravir or remdesivir.

Table III. Medication profile of favipiravir in hospitalized COVID-19 patients

Profile	Severity			Total (n=250)
	Mild (n=90)	Moderate (n=101)	Severe (n=59)	
Dosage of favipiravir				
Without loading dose	37 (41.11%)	11 (10.89)	2 (3.39%)	50 (20%)
With loading dose	53 (58.89%)	90 (89.11%)	57 (96.61%)	200 (80%)
Duration of therapy				
7 days	28 (31.11%)	45 (44.55%)	22 (37.29%)	95 (38%)
8-14 days	59 (65.56%)	52 (51.48%)	34 (57.63%)	145 (58%)
>14 days	3 (3.33%)	4 (3.96%)	3 (5.08%)	10 (4%)

Table IV. Favipiravir clinical outcome based on disease severity.

Parameter	Means of favipiravir use (n=250)		*p-vale*
	Before	After	
Temperature (Celcius)			
Mild (n=90)	36.55 ± 0.67	36.23 ± 0.24	0.0001
Moderate (n=101)	36.81 ± 0.61	36.21 ± 0.24	0.0001
Severe (n=59)	37.03 ± 0.80	36.23 ± 0.27	0.0001
Respiratory rate (x/minutes)			
Mild (n=90)	21.13 ± 1.98	20.20 ± 0.60	0.0001
Moderate (n=101)	21.69 ± 2.59	20.37 ± 1.07	0.0001
Severe (n=59)	23.42 ± 4.03	20.37 ± 1.51	0.0001
Symptom of Cough (sign-test)			
Mild (n=90)			0.0001
Moderate (n=101)			0.0001
Severe (n=59)			0.0001

Severe cases were treated with a regimen that included vitamins C, B1, D, azithromycin 500mg/day for 5-7days or levofloxacin 750mg/day for 5-7 days for suspected bacterial infection, favipiravir or remdesivir, and dexametasone for patients on ventilators (Burhan *et al*., 2020).

Favipiravir was provided in the form of a 200 mg film-coated tablet and administered orally. In this study, most patients (n=200; 80%), primarily those with moderate disease severity ((n=90; 89.11%), received favipiravir with a loading dosage regimen 1600 mg/12h on the first day, followed by 600 mg/12h until the end of therapy (Table III). Only 20% (n=50) of patients were given favipiravir without a loading dose (600 mg/12h daily until therapy completion). Patients with mild symptoms and a hospital stay of 8-14 days constituted the majority of those prescribed favipiravir (n=59; 65.56%). While the EUA stipulates favipiravir use for up to 7 or 14 days, based on clinical judgement, 4% of patients (n=10) who took the medication for more than 14 days deviated from the standards (BPOM RI, 2020).

Evaluation of clinical outcomes of favipiravir therapy

The efficacy of favipiravir on COVID-19 patients was evaluated by comparing clinical symptoms, including temperature, respiratory rate, and coughing, before and after seven days of treatment. The analysis was stratified according to the severity of COVID-19: mild, moderate, and severe. Outcomes were categorized based on symptom severity to minimize bias, given that clinical conditions differ in each degree of symptoms, and symptom severity may influence patients' clinical improvement (Mikkelsen & Abramoff, 2022). Clinical condition severity was determined from medical record information; however, some records were incomplete. In such cases, we classified patients according to their condition upon hospital admission, referring to the Clinical Management Guidelines for the Management of COVID-19 in Health Service Facilities issued by the Minister of Health Republic of Indonesia in 2021.

The average temperature for mild COVID-19 patients prior to favipiravir treatment was 36.55 ± 0.67, reducing to 36.23 ± 0.23 post-treatment (p=0.0001) (Table IV). Similarly, the average temperature in patients with moderate COVID-19 reduced from 36.70±0.5 before treatment to 36.25 ± 0.27 after treatment (p=0.0001). In severe cases, the average temperature of COVID-19 patients before and after favipiravir medication was 37.03 ± 0.80 and 36.23 ± 0.27 (p=0.0001), suggest that that favipiravir can effectively reduce the temperature in patients with mild to severe COVID-19.

The mean respiratory rate (RR) for mild COVID-19 patients before favipiravir treatment was 21.13 ± 1.98, reduced to 20.20 ± 0.60 after therapy (p=0.0001). The mean respiratory rate in patients with moderate COVID-19 was 21.70 ± 2.60 before treatment and 20.38±1.08 after treatment (p=0.0001). The mean respiratory rate in severe COVID-19 patients was 23.42 ± 4.03 before treatment and 20.37 ± 1.51 after treatment (p=0.0001), indicating the difference in respiratory rate values before and after favipiravir use in patients from mild to severe. The cough parameter yielded p-values 0.0001 for mild, moderate, and severe cases, indicating statistically significant differences in cough symptoms of cough before and after the favipiravir treatment across all severity levels (Table IV). The majority of patients treated with favipiravir at the Banyumas district hospital were of moderate severity. This is because Banyumas Regency hospitals, being secondary-level healthcare facilities, were primarily used to care COVID-19 patients in this research. As a result, the great majority of COVID-19 patients of varying disease severity. The majority of patient in this study were male, consistent with research conducted by (H. Cai, 2020), which indicates that the incidence of COVID-19 was 67% higher in men than in women. This could be attributed to chromosomal, hormonal, and behavioral factors, with men potentially more susceptible to COVID-19 due to these variables. Conversely, women may be better protected due to the presence of an X chromosome and sex hormones such as progesterone, which are critical role for innate and adaptive immunity (Her *et al*., 2022). Behaviorally, men may have a higher exposure risk to the virus due to smoking habits, which could make lung cells more susceptible to SARS-CoV-2 infection through the increase of the ACE-2 molecule (Achidsti *et al*., 2021).

In patients of moderate severity, the most represented age group in the favipiravir-treated cohort was 46-55 years. This aligns with the findings of Biswas *et al.*, (2021), which suggested that patients aged 47-59 years have a higher likelihood of fatality upon contracting the corona virus. This could be attributed to the declining immunity with age, which increase susceptibility to infections. Consequently, individuals within this age range are more susceptible to the SARS-CoV-2 virus (Hu *et al*., 2021).

The incubation period for COVID-19 was typically three to fourteen days, during which time white blood cells and lymphocytes counts remain normal or slightly reduced, and the patient is asymptomatic. The virus then spreads through the bloodstream, primarily to ACE2-expressing organs, leading to the manifestation of moderate symptoms. Four to seven days after the onset of symptoms, the patient's health begins to deteriorate, manifested by the onset of dyspnea, reduced lymphocytes, and progressing lung lesions. Without appropriate treatment during this phase, serious complications such as acute respiratory distress syndrome (ARDS), sepsis, and other conditions may develop (Hu *et al*., 2021).

Pneumonia is the most prevalent finding on chest X-ray in confirmed COVID-19 patients (Table II). The abnormalities detected in these chest X-rays often indicate the presence of bronchitis and pneumonia. The clinical features of COVID-19 pneumonia typically include inflammation and coagulopathy, leading to severe acute respiratory syndrome and a significant fatality rate ((Hu *et al*., 2021). In the early stages, or in indiciduals with mild symptoms, a chest X-ray, used as an initial diagnostic procedure for suspected COVID-19 cases, may appear normal (Hu *et al*., 2021). As COVID-19 typically presents clinically as a respiratory disease akin pneumonia, the most frequent imaging result is pneumonia, accounting for 72,9% of cases (Susilo *et al*., 2020).

Hypertension and diabetes mellitus are the most common comorbidities. Both hypertension and type 2 diabetes have been linked to the prognosis of COVID-19 (Lippi, Wong and Henry, 2020; Guan *et al.*, 2020; Hosseinzadeh *et al.*, 2021). Although the exact mechanismes underlying this relationship are not fully understood, one theory proposes the involvement of endothelial dysfunction and an imbalance in the renin-angiotensin system (RAS). SARS-CoV-2 enters the body via ACE2 receptors, resulting in downregulated ACE2, thereby diminishing its catalytic activity in the RAS. When ACE2 levels are

low, angiotensin II levels rise, leading to pro-oxidative and pro-inflammatory effects. Angiotensin II overexpression induces endothelial dysfunction and a cytokine storm, which leads to pulmonary, inflammatory, and hematological complications in COVID-19 patients. Elevated levels of angiotensin II also increase the formation of reactive oxygen species (ROS) via the Angiotensin Type 1 Receptor (AT1R). Additionally, immune cells produce ROS in response to stimulation by angiotensin II (Muhamad *et al*., 2021).

Increased levels of angiotensin II expression and excessive ROS production in individuals with concomitant diabetes mellitus can lead to insulin resistance, hyperglycemia, and vascular endothelial injury. These conditions increase the risk of cardiovascular events, thromboembolism, and disseminated intravascular coagulation (DIC). Infection can also increase the clotting factors such as fibrinogen and D-dimer, leading to increased blood viscosity, vascular endothelial damage, and subsequently cardiovascular events, thromboembolism, and DIC (Lim *et al*., 2020).

Clinical symptoms were observable conditions in patients. To evaluate the effects of favipiravir treatment, the Wilcoxon test was used, which considered patient medical records, including temperature and respiratory rate data, before and after favipiravir treatment. The Sign Test was used to evaluate qualitative symptoms of COVID-19 patients, assessing the effects of favipiravir on cough symptoms, again based on patient medical record data before and after treatment. These analysis revealed that favipiravir had significant impact on the clinical symptoms—temperature, respiratory rate, and cough—of patients with mild, moderate, and severe COVID-19, with a p-value of of 0.001. These results align with the finding of (Chen *et al*., 2020), who reported that favipiravir improved fever and cough symptoms in COVID-19 patients. Favipiravir, an RNA-dependent RNA polymerase (RdRp) inhibitor, inhibits the activity of RNA polymerase, thereby halting viral replication. The subsequent reduction in viral load and a favourable immune response are indicators of clinical recovery (Kramer *et al*., 2020).

The limitations of this study include the potential influence of other concurrent medications on the observed improvement in symptoms such as fever, cough, and shortness of breath in individuals treated with favipiravir. Paracetamol was frequently used to manage fever symptoms. Despite those limitation, the role of favipiravir to the clinical outcome of COVID-19 was deemed to be effective.

CONCLUSION

The use of favipiravir across mild, moderate, and severe levels of COVID-19 may improves the clinical symptoms of COVID-19 patients as reflected in improvements in cough symptoms, respiration rate, and body temperature.

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