BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 14, Number 2, October 2025 | Pages: 1219-1223 | DOI: 10.14421/biomedich.2025.142.1219-1223 ISSN 2540-9328 (online)

Cost Effectiveness Analysis of Favipiravir and Oseltamivir as Antiretroviral Covid-19 of Patients in Bogor Cisarua Lung Hospital

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Manuscript received: 14 April, 2025. Revision accepted: 04 December, 2025. Published: 11 December, 2025.

Abstract

Favipiravir is a type of RNA-dependent RNA polymerase (RdRp) inhibitor. Favipiravir is converted by host enzymes to T-705-ribofuranosyl 5′-triphosphate and may act as a nucleotide analogue that selectively inhibits viral RNA-dependent RNA polymerase or causes lethal mutagenesis upon insertion into viral RNA without cytotoxicity in mammalian cells. Oseltamivir is part of the neuraminidase inhibitors (NAIs) group which has a mechanism of action by inhibiting viral neuraminidase. Most of the alternative therapies for Covid-19 require pharmacoeconomic studies, especially regarding cost-effectiveness analysis which is useful in balancing patient expenses by determining treatment alternatives that represent the best health outcomes at a more affordable cost. The aim of this study was to compare the cost effectiveness of the antiretrovirals Favipiravir and Oseltamivir. This research method used a descriptive analytic cross-sectional design and data collection was carried out retrospectively from the medical records of Covid-19 sufferers while detailed data on medical expenses were obtained from the finance department of inpatients at Cisarua Pulmonary Hospital, Bogor for the period September-October 2022. Sample of 80 patients consisted of 40 patients using Favipiravir and 40 patients using Oseltamivir.The parameters used in this research are direct medical costs (which include doctor visit costs, treatment room costs, laboratory costs and drug costs) while the effectiveness uses a negative RT PCR value. The results showed that in patients using Favipiravir with an average length of treatment 6.525 days, the total cost was Rp. 9,930,327/patient and Cost-Effectiveness Ratio (RP/day/patient) Rp. 1,521,899.195, whereas in patients using Oseltamivir with an average length of treatment 7.925 days, the total cost was IDR. 12,368,397/patient and Cost-Effectiveness Ratio (Rp/day/patient) IDR. 1,560,681,009. It can be concluded that Favipiravir is more cost effective than Oseltamivir.

Keywords: COVID-19; Favipiravir; Effective and Efficient; Oseltamivir.

INTRODUCTION

Corona Virus Diseases 2019 (COVID-19) is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARCoV-2). SARCoV-2 is transmitted by direct contact with the patient through droplets when coughing or sneezing, as well as hands touching the mouth, nose, and eyes after touching objects contaminated with the virus. It first discovered on December 31, 2019. In 3 days, the number of patients with these cases amounted to 44 and has continued to grow to date, amounting to millions of cases. Initially, epidemiological data showed 66% of patients were related to one seafood market or fresh market in Wuhan, Hubei Province, China. Isolate samples from patients were studied, with results showing the presence of coronavirus infection, a new type of -coronavirus named novel Coronavirus. On March 11, 2020, WHO announced that COVID-19 had become a worldwide pandemic (Lapostolle F et al. 2020, Lingeswaran M et al. 2020, Bishnu P. D. et al. 2020, Suresh Kumar VC et al. 2020, Di Gennaro F et al. 2020)

The first COVID-19 case in Indonesia was announced on March 2, 2020, or about 4 months after the first case in China (Lingeswaran M et al. 2020). At the beginning, there were hundreds of cases added, and until now, the addition of cases has reached millions. At the time, there were currently no specific therapies or treatments for COVID-19. Nevertheless, some potential drugs have been used for people with COVID-19, although they are still in test drug status, and the results show good effectiveness (Suresh Kumar VC et al. 2020). For acute COVID-19 conditions and molecular detection methods, NAAT (Nucleid Acid Amplification Test) examinations, including RT-PCR examinations of COVID-19 patients who are hospitalized, show positive results for antivirals such as chloroquinphosphate, hydroxychloroquine, Favipiravir, Oseltamivir, remdesivir, and combinations between lopinavir and ritonavir (Suresh Kumar VC et al. 2020, Di Gennaro F et al. 2020)

Favipiravir is a type of RNA- dependent RNA polymerase (RdRp) inhibitor (Zhu N, et al. 2019). On February 14, a clinical trial of favipiravir for the treatment of COVID-19 was initiated by the Clinical Medical Research Center of the Third People's Hospital of Shenzhen. Preliminary results from a total of 80 patients (including the experimental group and the control group) showed that favipiravir had a stronger effect compared to lopinavir and ritonavir. There were no adverse reactions or significant side effects in the favipiravir treatment group compared to the lopinavir/ritonavir group (Suresh Kumar VC, et al. 2020). Oseltamivir is part of the class of neuraminidase inhibitors (NAIs), which have a mechanism of action by inhibiting viral neuraminidase and inhibiting the release of virus particles from infected cells so as to reduce the spread of the virus in the airway (Susilo A,et al. 2019. Y Furuta, et al. 2017, Uyeki TM 2018)

This COVID-19 disease requires a very large hospitalization cost of around Rp. 17,808,650 per patient; this value is calculated from the costs of drugs, treatments, laboratories, and radiology (Di Gennaro F et al. 2020). To meet the needs of quality and cost-effective health, the cost of treatment must be more affordable for the community and effective to get clinical results. Good is a negative RT-PCR value, and without drug side effects, health policy should go through appropriate economic evaluation (Lingeswaran M et al. 2020, Di Gennaro F et al. 2020). In August 2022, WHO no longer lists oseltamivir as clinical management of COVID-19 in health facilities. Study results show that oseltamivir is not effective against SARSCOV-2 in both in vitro testing and case reports in COVID-19 patients (Uyeki TM 2018).

In choosing the priority of the COVID-19 treatment strategy using antiretrovirals, favipiravir and oseltamivir, which provide the largest rational treatment outcomes, it is necessary to conduct a cost- effectiveness assessment analysis using the AEB method, which is very good to provide the best therapeutic recommendations, estimate health progress, and determine the most effective cost for COVID-19 treatment that relates the costs needed with the outcomes produced (Y Furuta, et al. 2017). This research is expected to provide benefits for the nation and state in determining the choice of quality and cost-effective antiretroviral drugs, especially as a consideration for policy formulation for the Ministry of Health in determining the cost of COVID-19 treatment and the resulting outcomes (Y Furuta, et al. 2017).

MATERIALS AND METHODS

We used pharmacoeconomic methods that involve effectiveness analysis with a cross-sectional research design (cross- sectional) and retrospective data search, the parameter measured was RT-PCR negative. Results are presented in a descriptive- analytic manner. The subjects of this study were inpatient COVID-19 patients using anti-retroviral favipiravir and oseltamivir at Cisarua Lung Hospital, Bogor, for the period September-October 2022.

The inclusion criteria in this study were adult Covid-19: p > 17 years, hospitalized patients diagnosed with moderate Covid-19 by doctors (positive RT- PCR value (CT < 40), patients undergoing treatment in July–December 2021, receiving antiretroviral therapy Favipiravir and Oseltamivir. The inclusion criteria were as follows: pregnant women, patients with unrecorded medical records of antiretrovirals used (type, dose, and frequency of administration) and no recorded PCR examination, patients admitted to the ICU during the study process, and patients who died during the study process.

The materials used were medical records and details of medical costs for COVID-19 patients at Cisarua Bogor Lung Hospital. The samples used were 80 medical records, consisting of 40 medical records of patients using favipiravir antiretrovirals and 40 medical records of patients using oseltamivir antiretrovirals.

In this study, researchers used the hypothesis test of the difference between two populations for the calculation of sample size with the formula:

$$n_1 = n_2 = \frac{(1{,}96\sqrt{2x0{,}82x0{,}11} + 0{,}842\sqrt{(0{,}82x0{,}11)+(0{,}75x0{,}25)})^2}{(0{,}89-0{,}75)^2}$$

$$= 79.90 \text{ patient} \sim 80 \text{ patient}$$

The medical record data obtained provides information about the characteristics of the patient (age, sex, length of treatment days, PCR value, drug name, dosage, and interval of administration). Cost data consists of direct costs obtained from financial documents, which include drug costs, laboratory costs, doctor consultation fees, and administrative costs.

Statistical data analysis using the Mann-Whitney method was used to compare the statistical significance of variability (see meaningful differences between kedua antiretroviral Favipiravir and Oseltamivir).

Pharmacoeconomic analysis, the average cost-effectiveness ratio (ACER) is the total cost divided by the output or effectiveness of each method. The ACER generated by each method is then compared; smaller values indicate a more cost- effective method compared to other methods. Grids are used to describe the cost position and outcome of alternative interventions.

Research Ethics Committee of Stikes Prima Indonesia, No. 206/EC/KEPK STIKES-PI/VIII/2022 has provided information that passed the ethical review for this study.

RESULTS AND DISCUSSION

Characteristics Of Research Subjects

Table 1. Characteristics of Covid 19 patients.

No	Variable	Category	Favipiravir n= 40	Oseltamivir n=40	Total n=80
1	Gender	Man	24	25	49
		Women	16	15	31
2	Place of residence	Bogor Regency	23	25	48
		Bogor City	4	7	11
		Outside Bogor	13	8	21
3	Length of Days	1 - 8	37	21	58
	Therapy	9 - 16	3	13	16
		17 - 24	0	6	6
4	PCR results	positif	30	39	74
	RS exit	Negatif	10	1	6

The study conducted in the COVID-19 treatment room of Cisarua Bogor Lung Hospital during a period of 2 months (September–October 2022), the number of hospitalized COVID-19 patients who met the inclusion criteria and exclusion criteria was 80 (research sample), consisting of 40 patients who received Favipiravir antiretroviral and 40 patients who received Oseltamivir antiretroviral. Table I Shows the characteristics of Inpatient COVID-19 patients in Cisarua Bogor Lung Hospital for the July– December 2021 period as follows: For sex characteristics, the 80 samples used showed that in Favipiravir antiretrovirals, male sex is 24% and female sex is 16%, while in Oseltamivir antiretrovirals, male sex is 25% and female sex is 15%. This is because men have higher levels of enzymes in the blood than women. Enzymes are a key factor for COVID-19 to infect human cells (Centers for Disease Control and Prevention, 2020 (9, 10). For patient residences, the 80 samples used showed that patients living in Bogor Regency by 48%, Bogor City by 11%, and Outside Bogor by 21% showed that there were patients living in Bogor City because of the hospital.

Cisarua Bogor Lung Hospital is a government referral hospital for treatment. Covid-19. Length of stay (LoS) is a duration of treatment of a patient in a health facility. LoS is one of the factors that affect the health care system and shows that the longer a patient's stay in the hospital, the greater the patient's need for resources, including medical personnel, materials, drugs, and equipment, resulting in increased costs therapy. The length of treatment days for patients taking Favipiravir antiretrovirals 1-8 days treatment period is 37%, 9-16 days is 3%, and there are no patients with 17-24 days of treatment, while in Oseltamivir antiretrovirals the treatment period is 1-8 days by 21%, 9-16 days by 13%, and 17-24 days by 6%. This is in accordance with research conducted in China, which shows that the length of days of treatment for COVID-patients 19 ranged from 4 to 53 days, and patients in the ICU ranged from 6 to 12 days (Song Y et al. 2020, Rees EM et al. 2020). Polymerase Chain Reaction (PCR) status when patients are discharged from the hospital: for patients using Favipiravir antiretrovirals, positive PCR results were 30% and negative PCR was 10%; for patients using Oseltamivir antiretrovirals, positive PCR results were 39% and negative PCR was 1% (Rees EM et al. 2020, Ye Q, Wang B MJ 2020). When viewed from the length of treatment days with the patient's PCR status at the time of discharge from the hospital, the best antiretroviral used for COVID-19 treatment therapy is Favipiravir, which is in accordance with the mechanism of action. Favipiravir is a type of RNA-dependent RNA polymerase (RdRp) inhibitor (Zhu N. et al. 2020).

On February 14, the clinical trial of favipiravir for the treatment of COVID-19 was initiated by the Clinical Medical Research Center of the Third People's Hospital of Shenzhen. Baseline results from a total of 80 patients (including experimental and control groups) showed that favipiravir had a stronger effect compared to lopinavir and ritonavir. There were no adverse reactions or significant side effects in the favipiravir treatment group compared to the lopinavir/ritonavir group (Suresh Kumar VC et al. 2020). For Oseltamir to provide less than maximum results than Favipiravir, this is in line with WHO's August 2022 revocation of the use of Oseltamivir for the treatment of COVID- 19.

Cost-effectiveness analysis is obtained by comparing the total cost with the effectiveness of the therapy obtained (output). Total Cost is a combination of total direct costs and indirect costs.

Direct Cost

Table 2. Compares The Cost-Effectiveness of Antiretroviral Administration.

No	Average	Favipiravir	Oseltamivir
1	Day of Care (day/patient)	6,525	7,925
2	Total Cost (IDR/patient)	9,930,327	12,368,397
3	Cost-Effectiveness Ratio (IDR/day/patient)	1.521.899,195	1.560.681,009

The direct cost component includes the total cost of treatment (room fee, drug fee, doctor's visit fee, and

laboratory fee). In Table 2, the results of the comparison of cost-effectiveness in the administration of antiretrovirals Favipiravir and Oseltamivir are as follows: In patients using Favipiravir, the average total cost is Rp. 9,930,327 per patient, while in patients using Oseltamivir, the average length of treatment days is Rp. 12,368,397 per patient.

Cost-Effectiveness Analysis

		Cost of Favipiravir Relative to Oseltamivir		
		lower	equals	Highher
Effectiveness of Favipiravir relative to Oseltamivir	Lower	A	B	C
	Equals	D	E	F
	Higher	G	H	I

Figure 1. Alternative Group Based on Total Cost-Effectiveness of Antiretroviral Administration.

Cost-effectiveness analysis is carried out using the Average Cost Effectiveness Ratio (ACER) and Cost-Effectiveness Grid formulas. In this study, the Incremental Cost Effectiveness Ratio (ICER) is not calculated because the results of the calculation of cost effectiveness are included in the table of areas C and G in the Cost-effectiveness Grid (meaning that Area G shows dominant results and definitely does not need to be selected). RIEB/ICER. Area C shows dominant results and does not need to be considered as an alternative, so it does not need to be included in the RIEB/ICER calculation. The ACER price is obtained from a comparison between the total cost of treatment and the effectiveness of therapy. The effectiveness of therapy was measured by the number of days per treatment (Afdal AF 2011).

Based on cost-effectiveness parameters, the ACER value based on the length of days from Favipiravir is Rp. 1,521,899,195 (proportion of treatment days: 6,525), while Oseltamivir is Rp. 1,560,681,009. In the Favipiravir group, the ACER price was lower than in the Oseltamivir group. This suggests that Favipiravir therapy is more cost-effective or has the most cost-effectiveness compared with Oseltamivir therapy.

CONCLUSIONS

Based on the results of this study, it can be concluded that the Favipiravir antiretroviral therapy group is more cost- effective in the treatment of COVID-19 compared to the Oseltamivir antiretroviral therapy group.

Acknowledgements: Praise and thank Allah SWT for all His mercy and pleasure so that the author can complete this writing process. The author would like to thank all parties who have played a role in this writing process, especially the Directorate General of Higher Education, Research, and Technology of the Ministry of Education, Culture, Research, and Technology who have funded this research.

Competing Interests: The authors declare that there are no competing interests.

Funding: This research received funding from Directorate General of Higher Education, Research, and Technology of the Ministry of Education, Culture, Research, and Technology.

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