*COST-EFFECTIVENESS ANALYSIS OF* REMDESIVIR AND FAVIPIRAVIR THERAPY FOR THE TREATMENT OF COVID-19 IN ADULT PATIENTS AT THE HAJJ REGIONAL GENERAL HOSPITAL, EAST JAVA PROVINCE

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**ABSTRACT**

Cases of *Coronavirus Disease* 2019 or COVID-19 from year to year show a tendency to increase spread worldwide, including Indonesia. COVID-19 is an infectious disease caused by a virus so redeliver and Favipiravir antiviral therapy is needed. This study compared the cost-effectiveness analysis of the drugs Ravipiravir and Remdesivir in COVID-19 disease at Haji Hospital Surabaya. This study compares observationally between 2 (two) alternatives using a hospital perspective and data collection carried out retrospectively in the period April 2021 to October 2021. The Cost Effectiveness *Analysis* method used is *the Cost-Effectiveness Ratio* (ACER). The results of the data obtained from the ACER cost-effectiveness analysis method in the Favipiravir group are Rp. 2,820,601.63 per day for length of stay and Rp. 6,485,071.79 per day for COVID-19-free time. While in the Remdesivir group Rp. 3,311,510.74 per day for the length of stay and Rp. 8,329,527.98 per day for COVID-19-free time. Meanwhile, the ICER analysis method is Rp. 6,195,280.50 per day for the length of hospitalization and Rp. 34,802,899 per day for COVID-19-free time. This study concludes that Favipiravir is more *cost-effective* than Remdesivir.

Keywords : *Cost-Effectiveness Analysis*, COVID-19, Ravipiravir, Remdesivir

1. **Introduction**

Cases of *Coronavirus Disease* 2019 or COVID-19 tend to increase rapidly spreading throughout Indonesia. WHO reported that in July 2021 it had reached 36,057,8392 cases of COVID-19 and 5,620,865 deaths worldwide (*Case Fatality Rate* / CFR 4.8%). 1The Ministry of Health reported that in November 2021 it had reached 4,246,802 confirmed cases of COVID-19 with 143,500 deaths in Indonesia (CFR 2%). 2

COVID-19 is an infectious disease caused by *Severe Acute Respiratory Syndrome* (SARS)*.* 3 COVID-19 is an infectious disease caused by a virus so antiviral therapy is needed. 5 Antivirals that can be used in people with moderate or severe symptoms are Remdesivir and Favipiravir. Both of these drugs are *prodrug* nucleotide analogues that can inhibit RNA *polymerase* from viruses and have shown in vitro activity against COVID-19. 7 The clinical manifestations of COVID-19 patients are broad in spectrum, with a division of about 80% of cases classified as mild or moderate, 13.8% experiencing severe illness, and as many as 6.1% of patients falling into a critical state. 4 Antivirals that can be used in people with moderate or severe symptoms are Remdesivir and Favipiravir.

According to the COVID-19 treatment procedures compiled by the Ministry of Health in 2020, it is divided into the management of asymptomatic people (OTG), people with mild, moderate, and severe symptoms. Especially for moderate to severe diseases, isolation must be carried out for 14 days in the hospital. According to the treatment procedures for COVID-19 compiled by the Indonesian Lung Doctors Association (PDPI) in 2020, Remdesivir with a dose of 200 mg IV drip (day 1) then therapy continued 1x100 mg IV drip (days 2-5 or days 2-10). While Favipiravir with a dosage of 200 mg with *a loading dose* of 1600 mg per 12 hours orally on the first day and continued 2x 600 mg on day 2 to day 5. 6

There are several studies comparing the therapeutic efficacy of Remdesivir and Favipiravir. Clinical uji has been performed that has shown an association of Remdesivir with a low increase in the frequency of side effects when compared to Favipiravir with clinical indicators of these patients improved significantly on the 7th and 14th days (72.6% and 86.5% in mild COVID-19 cases, 63.4% and 77.2% in moderate cases, as well as 46.6% and 60.4% in severe cases). 8 Puse of Favipiravir tends to be more promising for therapeutic and cost-effective effects, especially in low- and middle-income countries. This is one way of developing treatment and evaluating cost-effectiveness to inform appropriate resource allocation decisions. 7

In this study, it is necessary to conduct pharmacoeconomic testing to analyze the effectiveness of therapy in terms of cost efficiency to achieve treatment of rational. 9 several pharmacoeconomic methods have functions and *outcomes* with specific objectives, one of the methods that is in accordance with this study is the *Cost-Effectiveness Analysis* (CEA) method because this method compares costs and clinical *outcomes*, namely the effectiveness of treatment consisting of the length of stay or *length of stay*, laboratory results, and vital signs. 10

*Cost-Effectiveness Analysis* (CEA) is a method designed to assist health workers in identifying options determined among several alternatives by testing the ratio of cost differences and differences in health effectiveness. 1 1 Remdesivir administration, when comparing total medical expenses with *years of life saved* in a year, can save costs against standard care and prevent mortality. 12 So that in this study it is necessary to determine the effectiveness and efficiency of Remdesivir and Favipiravir antiviral treatment therapy with the CEA method to achieve maximum treatment in hospitals, especially in Indonesia.

1. **Method**

The research design used in this study is a non-experimental research design with a retrospective method. This study is observational by comparing between two alternatives using a hospital perspective and data collection carried out in the period from April 2021 to October 2021. In this study, the method used was CEA with clinical *outcomes,* namely the length of hospitalization and the recovery time of COVID-19.

The variables depending on this study are the total overall cost and effectiveness of treatment therapy. While the free variables are Remdesivir antiviral therapy and Favipiravir antiviral therapy.

The target population in this study is all COVID-19 patients treated at the Hajj General Hospital in Surabaya from April 2021 to October 2021. The sampling technique is carried out by total sampling. The sample in this study is part of the target population of the study object and has met the inclusion criteria with complete status data.

The study was conducted restrospectively where all patient cost data and COVID-19 patient medical record data were collected at the Hajj General Hospital in Surabaya in the period from April 2021 to October 2021. Data analysis in this study compared the total direct cost with the effectiveness of treatment between each COVID-19 therapy group (Favipiravir therapy group and Remdesivir therapy group) so that it can be known which of each of these groups is *cost effective* using the *Average Cost-Effectiveness Ratio* (ACER) method.

1. **Results of the discussion**
   1. **Sample Descriptive Data**

In this study, 211 patients were obtained, consisting of 72 COVID-19 patients with the use of Remdesivir (Remdesivir Group) and 139 COVID-19 patients with the use of Favipiravir (Favipiravir group) in accordance with the inclusion criteria. The exclusion criteria in this study are *non-comorbid* diseases such as penumonia, and hepatitis.

The basic characteristics of the study subjects were grouped by gender, age, level of education, occupation, financing system and disease history of the study subjects. Based on research, the number of male subjects (85 subjects) was more than that of female subjects (43 subjects) in the Favipiravir group. Meanwhile, the number of male subjects (43 subjects) was more than that of female subjects (29 subjects) in the Remdesivir group. Based on age criteria, patients with COVID-19 were obtained the most in the range of 51-60 years and at least 31-40 years from favipiravir and Remdesivir groups. This is in accordance with the research conducted in Dibali, where the most patients are in the range of 50 years to 70 years. 14 The relationship between work and COVID-19 risk is more widely viewed based on the likelihood of specific exposure, the degree of exposure, and the risk of occurrence. Based on the level of education regarding the occurrence of COVID-19, in this study it can be said that the higher the level of education, the better a person is in terms of dealing with the disease. The patient's participation to become a member of the Social Security Organizing Agency (BPJS) is determined by knowledge of information about BPJS, besides that there is also a personal ­*reference* factor, namely their own desire or the invitation of others to become BPJS participants.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristic | | Group | | | | | | Group Difference Test | | | |
| **Favipiravir (n : 139)** | | | **Remdesivir (n : 72)** | | | **P-value** | | **Conclusion** | |
| Frequency | | Percentage  (%) | | Frequency | Percentage  (%) | |  | |  |
| Gender | **Man** | 85 | | 40,3% | | 43 | 20,4% | | 0,840 | | no difference |
| **Woman** | 54 | | 25,6% | | 29 | 13,7% | |
| Age (years) | **18-30** | 19 | 9,0% | | 7 | | 3,3% | | 0.869 | | no difference |
| **31-40** | 16 | | 7,6% | | 9 | 4,3% | |  | |  |
| **41-50** | 27 | | 12,8% | | 15 | 7,1% | |
| **51-60** | 34 | | 16,1% | | 25 | 11,8% | |
| **61-70** | 42 | | 19,9% | | 16 | 7,6% | |
| Education Level | **Basis** | - | | 0,00% | | - | 0,00% | | 0,747 | | no difference |
| **Intermediate** | - | | 0,00% | | - | 0,00% | |
| **Above** | 44 | | 20,9% | | 22 | 10,4% | |
| **College** | 83 | | 39,3% | | 46 | 21,8% | |
| Work | **Work** | 96 | | 45,5% | | 54 | 25,6% | | 0,367 | | no difference |
| **Not Working** | 43 | | 20,4% | | 18 | 8,5% | |
| Payment Systems | **BPJS** | 55 | | 26,1% | | 37 | 17,5% | | 0,101 | | no difference |
| **Common** | 84 | | 39,8% | | 35 | 16,6% | |
| History of the disease | **Diabetes Mellitus** | 25 | | 11,8% | | 17 | 8,1% | | 0,315 | | no difference |
| **Hypertension** | 22 | | 10,4% | | 17 | 8,1% | |
| **Cardiovascular (CVD)** | 27 | | 12,8% | | 11 | 5,2% | |
| **Tubercolosis (tuberculosis)** | 3 | | 1,4% | | - | 0,00% | |
| **Asthma** | 1 | | 0,5% | | - | 0,00% | |
| **None** | 60 | | 28,4% | | 26 | 12,3% | |

**Table 1. Basic characteristics of the subjects of study**

**Table 2. Total cost (*Direct Medical Cost)***

|  |  |  |
| --- | --- | --- |
| Direct Medical Costs | Remdesivir Group | Favipiravir Group |
| The cost of antiviral drugs | IDR 2,172,835.42 | IDR 663,000.00 |
| Room Usage Fee | IDR 2,125,875.00 | IDR 1,807,539.57 |
| Laboratory Costs | IDR 3,232,347.00 | IDR 2,804,165.47 |
| External Lab Fees | IDR 13,432,428.89 | IDR 8,030,396.36 |
| Covid-19 Measures Cost | IDR 19,379,612.00 | IDR 13,853,349.79 |
| Cost of Nurse Actions | IDR 3,113,287.77 | IDR 4,467,763.89 |
| Administration Fee | IDR 23,750.00 | IDR 20,935.25 |
| Total Cost | **IDR 43,480,136.08** | **IDR 31,647,150.33** |

* 1. **Direct Medical Costs**

The costs in this study used *direct medical* costs, including the use of antiviral drug, room usage, laboratory costs, external lab costs, COVID-19 action costs, nurse action fees and administrative costs. The average total cost of direct medical treatment for COVID-19 patients during treatment at a hospital using the drug Favipiravir is Rp. 31,647,150.33 / patient and patients taking the drug Remdesivir is Rp. 43,480,136.08/patient (Table 2). From table 2 it can be seen that the highest average amount of direct medical costs is the remdesivir group, this is in accordance with the research conducted *by Leslie et al* said that the highest total cost is the remdesivir group compared to standard nurse therapy in this case the use of antibiotics and other antivirals. 12

* 1. **The effectiveness of treatment**

In this study, the effectiveness of treatment was assessed based on comparing the length of treatment and the disappearance of COVID-19 symptoms in patients taking Favipiravir with patients taking Remdesivir. The average length of treatment of patients taking Favipiravir was 11.22 days and patients taking Remdesivir was 13.13 days. While the duration of disappearance of COVID-19 symptoms on average patients who took Favipiravir was 4.88 days and patients who took Remdesivir were 5.22 days,

According to research Lam et al said lama treatment average patient for 10 days plus at least 3 days free of COVID-19 symptoms such as fever and other respiratory disorders. 15 while the duration of disappearance of COVID symptoms is marked by the disappearance of common signs of COVID-19 including fever, dry cough, and weakness. Other complaints that patients usually experience include shortness of breath, sore throat, runny nose, reduced appetite, diarrhea, to reduced sensations of the sense of smell and sense of taste. 14

* 1. **ACER** Interpretation

The calculation of the ACER value is used to determine the cost per day that the patient must incur compared to its effectiveness. Effectiveness in this study was measured from the average length of hospitalization and the time of disappearance of COVID-19 symptoms from each therapy group. The average *Cost-Effectiveness Ratio* (ACER) results based on the length of hospitalization showed that the lowest ACER value was the Favipiravir antiviral group with an ACER value of Rp. 2,820,601.63 / day with an average length of stay of 11.22 days while the ACER value for the Remdesivir group is Rp. 3,311,510.74/day with an average length of stay of 13.13 days. ACER results based on the disappearance time of COVID-19 symptoms show that the lowest ACER value is the Favipiravir antiviral group with an ACER value of Rp. 6,485,071.79 / day with an average time of covid-19 symptom disappearance of 4.88 days while the ACER value for the Remdesivir group is Rp. 8,329,527.98/day with an average covid-19 symptom disappearance time of 5.22 days.

**Table 3. Calculation of *ACER Average Cost-Effectiveness Ratio* between Total Cost and Length of Hospitalization**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug Group | Total Cost (C) | Length of Treatment  Stay (E) | ACER (C/E) |
| Remdesivir | IDR 43,480,136.08 | 13.13 days | IDR 3,311,510.74 |
| Favipiravir | IDR 31,647,150.33 | 11.22 days | IDR 2,820,601.63 |

**Table 4. Calculation of *ACER Average Cost-Effectiveness Ratio* between Total Biava and Length of Loss of COVID-19 Symptoms**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug Group | Total Cost (C) | Long Lost Symptoms of COVID-19 (E) | ACER (C/E) |
| Remdesivir | IDR 43,480,136.08 | 5.22 days | IDR 8,329,527.98 |
| Favipiravir | IDR 31,647,150.33 | 4.88 days | IDR 6,485,071.79 |

From the *cost-effectiveness* analysis, it was found that the Favipiravir therapy group was more cost-effective compared to the Remdesivir therapy group, although the daily cost (ACER) of the Remdesivir therapy group was more expensive when compared to the Favipiravir therapy group, but when compared to its effectiveness (length of stay and time of disappearance of COVID-19 symptoms ) these costs will be different. The Favipiravir antiviral therapy group was more effective with a length of stay of 11.22 days at a lower cost expenditure compared to the Remdesivir antiviral with a length of stay of 13.13 days.

The results of determining the alternative positioning of COVID-19 treatment based on the Cost-Effectiveness Diagram, it is known that in the length of treatment and the duration of disappearance of COVID-19 symptoms Favipiravir's position lies in quadrant II which means that Favipiravir has high effectiveness at a low cost compared to Remdesivir.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Cost of Remdesivir against Favipiravir | | |
| Lower | same | Higher |
| Effectiveness of Remdesivir against Favipiravir | Higher | **Favipiravir**  *(Dominant)* | + | +/- *(Trade Off)* |
| same | + | *Arbitary* | - |
| Lower | *+/- (Trade off)* | - | *(Dominated)* |

**Table 5. *Cost-effectiveness Grid* Use of Favipiravir group with Remdesivir group based on Length of Hospitalization and Duration of disappearance of COVID-19 symptoms**

**Figure 1.** ***Cost-effectiveness Grid* Use of Favipiravir group with Remdesivir group based on Length of Hospitalization.**

**Table 6.** **Simulation of Average Cost Against ACER Sensitivity using Favipiravir and Remdesivir Based on Length of Hospitalization.**

|  |  |  |
| --- | --- | --- |
| Average Medical Costs | Remdesivir Group | Favipiravir Group |
| Early ACER | | |
| ACER (C/E) | 3,311,510.74 /day | 2,820,601.63/day |
| ACER no action fee | | |
| ACER (C/E) | 1,014,930.44 /day | 1,187,703.80 /day |
| ACER with no room usage fee | | |
| ACER (C/E) | 3,149,601.00 /day | 2,659,501.85 /day |
| ACER with no room usage fees and action fees | | |
| ACER (C/E) | 1,436,508.86 /day | 1,026,604.02 /day |

**3.5 SENSITIVITY ANALYSIS**

The next stage of analysis is a sensitivity analysis can be seen in table 6. The way to analyze sensitivity is to recalculate the ACER of each alternative output by simulating by issuing one or more cost variables so that the value can change. The expenditure of one variable cost is made on the cost of using the room and the cost of the action. From the results of the sensitivity analysis, it shows that the ACER value from using Favipiravir without involving room usage fees and action fees is Rp. 1,026,604.02 / day based on the length of hospitalization, while the ACER value from using Remdesivir without involving room usage fees and action fees is Rp. 1,403,508.86 / day, where the difference from the cost is Rp. 376,904.85 / day. The results of the sensitivity analysis show that the ACER from the use of Favipiravir does not involve room usage fees and action costs, namely Rp. 2,360,347.76 / day based on the disappearance of COVID-19 symptoms, while the value of ACER and the use of Remdesivir without involving room usage fees and action fees are Rp. 3,613,287.61 / day, where the difference from the simulation fee is Rp. 1,252,939.85 / day. The results with this difference can be considered by practitioners that Favipiravir can be used as an alternative antiviral that can be used in the treatment of COVID-19.

1. **Conclusion**

*Cost-effectiveness Grid* results showed dominant results in the Remdesivir group for patients with COVID-19 treatment. The average total direct medical cost of the Favipiravir antiviral group was lower than that of the Remdesivir antiviral group. ACER results show that Favipiravir antivirals are more cost-effective than Remdesivir antivirals in the treatment of COVID-19. There was a significant difference in total direct medical costs between the Favipiravir group and the Remdesivir group.

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