

## Cost-effectiveness analysis of COVID-19 treatment for hospitalized patients: a healthcare provider perspective in Batam, Indonesia

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### ABSTRACT

The COVID-19 pandemic is a global crisis that has continued to impact health, population, and the economy. Therefore, this study aims to evaluate the cost-effectiveness of COVID-19 treatment for hospitalized patients from the perspective of healthcare providers. An observational study was conducted retrospectively by collecting data from medical records of hospitalized COVID-19 patients between April 1 and June 30, 2021. The effectiveness of the therapy was evaluated based on COVID-19 treatment guidelines in Indonesia, by calculating the number of recovered patients within 14 days. The study only considered the direct medical costs of treatment, while the cost-effectiveness was analyzed using Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER). The results showed that the average direct cost of COVID-19 treatment per patient was approximately IDR 28,114,775.52 ± IDR 16,352,597.11. The most effective treatment was Favipiravir + Levofloxacin + N-acetylcysteine, followed by Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine, with 97% and 91% effectiveness, respectively. The ACER of COVID-19 treatments ranged from Rp 15,596,973 to 58,140,864, while the ICER was mainly located in the South East Quadrant, with Favipiravir + Levofloxacin + N-acetylcysteine being dominant compared to other treatments, saving IDR 161,653.97 to 33,870,916.17 per recovered patient. Effective COVID-19 treatments for hospitalized patients provide good value for the health system. However, this study was limited by the unavailability of the most recent information on the rapidly evolving pandemic.

### Key words:

COVID-19; cost-effectiveness analysis; inpatient treatment; hospitalized patient.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, Hubei Province, China, in late December 2019. It is a highly contagious viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a deadly disaster affecting world demographics, culminating in more than 6 billion deaths<sup>1</sup>. SARS-CoV-2 has spread rapidly worldwide in a short period, forcing the World Health Organization (WHO) to declare it a global pandemic on March 11, 2020<sup>2</sup>.

Coronavirus is an enveloped, positive, single-stranded RNA virus and as the name suggests, it belongs to the Orthocoronavirinae subfamily, whose members have characteristic crown-like spines on their surface<sup>3</sup>. The disease has flu-like symptoms that can become severe in individuals who are at high risk. The main symptoms are fever, cough, fatigue, mild shortness of breath, sore throat, headache, conjunctivitis, and gastrointestinal problems<sup>4</sup>.

Since the first case was reported on March 2, 2020, up to November 16, 2022, Indonesia has recorded a total of 6,573,805 confirmed cases of COVID-19, wherein 159,199 (2.4%) died, and 6,360,832 (96.8%) were declared cured. The confirmed cases are currently being treated and isolated in hospitals, designated isolation facilities, and through self-isolation<sup>5</sup>.

Indonesia established the National Healthcare Insurance (BPJS Kesehatan) as its national health insurance system in 2014. BPJS Kesehatan is a part of the National Social Security System (SJSN) which is designed to meet the basic healthcare needs of all citizens<sup>6</sup>. For paying system, BPJS Kesehatan has released technical instructions using INA-CBG (Indonesian Case-Based Groups)

tariff packages for covering treatment, including COVID-19. It was designed as a package-based payment system for the diagnosis and drug treatment procedures given to a patient. However, the pricing of drugs in these packages is fully determined by market mechanisms, which may lead to increased fees due to rising drug prices<sup>7</sup>. The INA-CBGs package system also causes a disparity in the cost of health services when claiming benefits. Consequently, to avoid such potential biases, this study was conducted solely from the perspective of healthcare providers.

The understanding of COVID-19 and its treatment was initially limited in the early stages of the pandemic, thereby creating the urgency to mitigate this emerging disease with experimental therapies and drug repurposing<sup>8</sup>. Several treatments have been proposed recently to treat COVID-19, including Remdesivir, Favipiravir, Paxlovid-Ritonavir, and Molnupiravir as antiviral, and monoclonal antibodies such as Tocilizumab and Baricitinib. Additionally, steroid treatments namely Dexamethasone have been used to manage severe symptoms and reduce mortality rates<sup>9</sup>.

An economic evaluation was explored to evaluate the effectiveness by considering clinical and cost parameters. This study evaluated the cost-effectiveness of COVID-19 treatment in general public hospitals in Batam, Indonesia based on the healthcare provider perspective. The evaluation considered the Average Cost Effectiveness Ratio (ACER) and Incremental Cost Effectiveness Ratio (ICER) to assess whether the benefits of treatment justify its additional costs. The results obtained will serve as a recommendation for policymakers to adopt this treatment as a viable therapy for COVID-19 specifically in Batam and Indonesia in general.

## METHODS

An observational study was conducted retrospectively to collect data from medical records and hospital financial data of hospitalized COVID-19 patients at General Hospital in Batam, Indonesia, from April 1 to June 30, 2021. Inclusion criteria were confirmed COVID-19 inpatients aged 12-64 and categorized as intermediate to high severity according to the medical record. Dead patients and those who did not complete the therapy, or had no complete medical record were excluded. The sample size was determined using the Slovin formula<sup>10</sup> with a total population of 495 and 102 eligible patients who were selected with simple random sampling. The effectiveness of the therapy was measured based on the COVID-19 treatment protocol, which is achieved by counting recovered patients within 14 days<sup>11</sup>. The recovered patients were described as individuals who have fulfilled specific criteria, including obtaining a negative test result and experiencing the absence of symptoms. Since the analysis focused on the healthcare provider perspective, only direct medical costs of COVID-19 treatment were considered. These included COVID-19 therapy, comorbidity, and non-COVID-19 therapy as well as medical devices, services, including doctor and other health worker incentive, laboratory, and radiology services. Direct non-medical costs, such as productivity and time costs to patients and families, were not included.

Additionally, hospital room services were excluded from this study due to the varying costs associated with different classes of hospital rooms for inpatients. These raise concerns that such differences may culminate in biased outcomes related to the costs of COVID-19 therapy. In this perspective, all costs of

hospitalized patients were derived from medical records and hospital financial data. Ethical approval was obtained from the Ethics Committees of Jambi Health Polytechnic Ministry of Health with protocol code number: LB.02.06/2/165/2022 and date of approval: 31<sup>st</sup> May 2022. The descriptive statistics presented in the study aimed to provide a comprehensive overview of the baseline characteristics of the selected patients. Monetary values were reported in Indonesian Rupiah (IDR) and no discount rate was applied. The cost-effectiveness was analyzed using *Average Cost-Effectiveness Ratio* (ACER) and *Incremental Cost-Effectiveness Ratio* (ICER) as determined according to the formula.

$$ACER = \frac{Cost(IDR)}{Effectiveness (\%)}$$

$$ICER = \frac{Cost A - Cost B (IDR)}{Effectiveness A - Effectiveness B (\%)}$$

## RESULT

Based on the inclusion criteria, the study sample comprised 102 patients, the majority of whom were female (n = 55), and the age group was 15-64 years old (n = 99). Additionally, the majority of patients had a length of stay (LOS) ranging from 7-14 days (n = 90), and the treatment adopted for their therapy was Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine (n = 42). Detailed information about the characteristics of the patients is described in Table 1.

The average direct cost of COVID-19 treatment per patient was estimated to be IDR 28,114,775.52± IDR 16,352,597.11 as shown in Table 2. Compared to other components in direct medical costs, the results showed that the most remarkable contributions to the total treatment cost were from non-COVID-19 therapy and disposable medical devices in COVID-19 treatment groups, followed by

Immunoglobulin M/G + Remdesivir + Favipiravir + Levofloxacin + N-acetylcysteine, and medical services, respectively.

**Table 1.** Patient Characteristics

| Category                    | Distribution                                                                    | Frequency<br>(n=102) | Percentage<br>(%) |
|-----------------------------|---------------------------------------------------------------------------------|----------------------|-------------------|
| Gender                      | Female                                                                          | 54                   | 52.94             |
|                             | Male                                                                            | 48                   | 47.06             |
| Latest Education Background | None                                                                            | 19                   | 18.62             |
|                             | Elementary School                                                               | 1                    | 0.98              |
|                             | Junior High School                                                              | 5                    | 4.91              |
|                             | Senior High School                                                              | 58                   | 56.86             |
|                             | Bachelor Degree                                                                 | 19                   | 18.63             |
| Age (years)                 | 12 – 14                                                                         | 3                    | 2.94              |
|                             | 15 – 64                                                                         | 99                   | 97.06             |
| Length of Stay (days)       | <7 days                                                                         | 7                    | 6.86              |
|                             | 7-14 days                                                                       | 88                   | 86.28             |
|                             | >14 days                                                                        | 7                    | 6.86              |
| Marital Status              | Married                                                                         | 86                   | 83.31             |
|                             | Not Married                                                                     | 16                   | 16.69             |
| Employment Status           | Self-employed                                                                   | 38                   | 37.25             |
|                             | Civil Servant                                                                   | 17                   | 16.66             |
|                             | Student                                                                         | 8                    | 7.85              |
|                             | House Wife                                                                      | 39                   | 38.24             |
| COVID-19 Therapy            | Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine                    | 11                   | 10.78             |
|                             | Favipiravir + Azithromycin + N-acetylcysteine                                   | 42                   | 41.18             |
|                             | Favipiravir + Levofloxacin + N-acetylcysteine                                   | 31                   | 30.39             |
|                             | Remdesivir + Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine       | 12                   | 11.76             |
|                             | Immunoglobulin M/G + Remdesivir + Favipiravir + Levofloxacin + N-acetylcysteine | 6                    | 5.89              |
|                             |                                                                                 |                      |                   |
|                             |                                                                                 |                      |                   |

**Table 2.** Total Direct Cost of Covid- 19 Treatments (in Indonesian Rupiah/ IDR)

| COVID-19 Treatment                                                                    | COVID-19 Therapy        | non-Covid Therapy + Medical Device | Medical Services        | Laboratory             | Radiology             | Total Cost            | Average Cost         |
|---------------------------------------------------------------------------------------|-------------------------|------------------------------------|-------------------------|------------------------|-----------------------|-----------------------|----------------------|
| Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine (n=11)                   | 22,665,322<br>(10.90%)  | 108,661,761<br>(52.26%)            | 53,959,000<br>(25.95%)  | 19,747,000<br>(9.50%)  | 2,890,000<br>(1.39%)  | 207,923,083<br>(100%) | 18,902,098.45        |
| Favipiravir + Azithromycin + N-acetylcysteine (n=42)                                  | 41,233,170<br>(6.56%)   | 344,541,550<br>(54.81%)            | 161,744,500<br>(25.73%) | 0,232,000<br>(11.17%)  | 10,880,000<br>(1.73%) | 628,631,220<br>(100%) | 14,967,410           |
| Favipiravir + Levofloxacin + N-acetylcysteine (n=31)                                  | 35,527,797<br>(7.58%)   | 243,598,686<br>(51.94%)            | 123,498,500<br>(26.33%) | 58,386,000<br>(12.45%) | 7,990,000<br>(1.70%)  | 469,000,983<br>(100%) | 15,129,063.97        |
| Remdesivir + Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine (n=12)      | 22,585,723<br>(4.40%)   | 365,189,025<br>(71.21%)            | 87,570,000<br>(17.08%)  | 32,399,000<br>(6.32%)  | 5,100,000<br>(0.99%)  | 512,843,748<br>(100%) | 42,736,979           |
| Immunoglobulin M/G + Remdesivir + Favipiravir + Levofloxacin + N-acetylcysteine (n=6) | 107,497,706<br>(36.68%) | 86,039,251<br>(29.36%)             | 59,552,000<br>(20.32%)  | 37,281,000<br>(12.72%) | 2,660,000<br>(0.91%)  | 293,029,957<br>(100%) | 48,838,326.17        |
| <b>Average</b>                                                                        |                         |                                    |                         |                        |                       |                       | <b>28,114,775.52</b> |
| <b>Standard of Deviation (SD)</b>                                                     |                         |                                    |                         |                        |                       |                       | <b>16,352,597.11</b> |

The effectiveness of COVID-19 treatments was measured by counting recovered patients within 14 days of treatment. The most effective treatment was Favipiravir + Levofloxacin + N-acetylcysteine, followed by Favipiravir + Levofloxacin + Azithromycin + N-

acetylcysteine, with percentages of 97% and 91%, respectively as shown in Table 3. The average Cost-Effectiveness Ratio (ACER) ranged from Rp 15,596,973 - 58,140,864, the lower the value, the greater the cost-effectiveness (Table 4).

**Table 3.** Effectiveness of COVID-19 Treatments

| No | Types of COVID-19 Treatment                                                     | Total Patient | Patient Recovered | Effectiveness | Percentage |
|----|---------------------------------------------------------------------------------|---------------|-------------------|---------------|------------|
| 1  | Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine                    | 11            | 10                | 0.91          | 91%        |
| 2  | Favipiravir + Azithromycin + N-acetylcysteine                                   | 42            | 35                | 0.84          | 84%        |
| 3  | Favipiravir + Levofloxacin + N-acetylcysteine                                   | 31            | 30                | 0.97          | 97%        |
| 4  | Remdesivir + Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine       | 12            | 9                 | 0.75          | 75%        |
| 5  | Immunoglobulin M/G + Remdesivir + Favipiravir + Levofloxacin + N-acetylcysteine | 6             | 5                 | 0.84          | 84%        |

**Table 4.** Average Cost Effectiveness Ratio (ACER) of COVID-19 Treatments

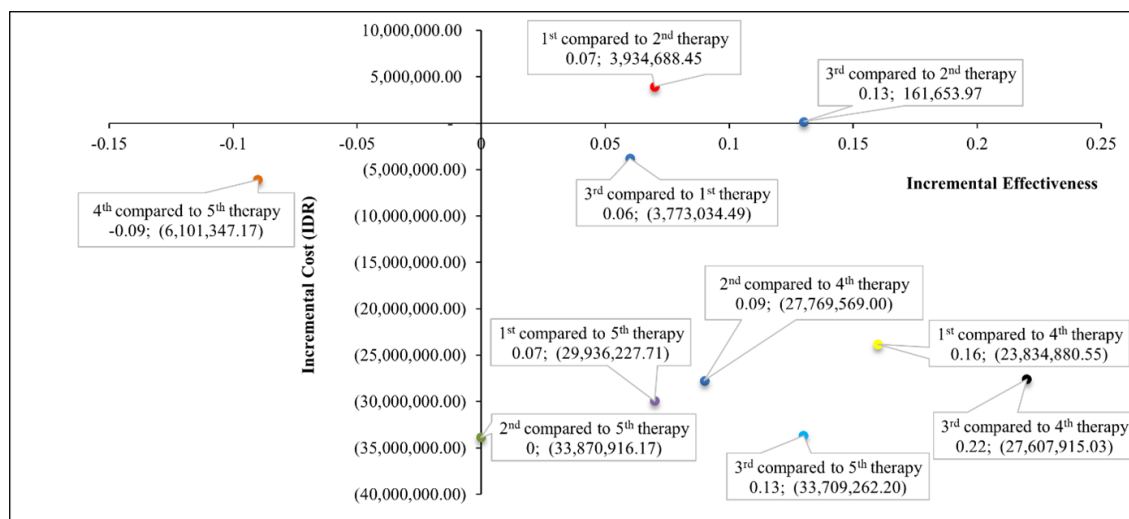
| No | Types of COVID-19 Treatment                                                     | Average Cost (C) | Effectiveness (E) | (ACER)     |
|----|---------------------------------------------------------------------------------|------------------|-------------------|------------|
| 1  | Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine                    | 18,902,098.45    | 0.91              | 20,771,536 |
| 2  | Favipiravir + Azithromycin + N-acetylcysteine                                   | 14,967,410       | 0.84              | 17,818,345 |
| 3  | Favipiravir + Levofloxacin + N-acetylcysteine                                   | 15,129,063.97    | 0.97              | 15,596,973 |
| 4  | Remdesivir + Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine       | 42,736,979       | 0.75              | 56,982,638 |
| 5  | Immunoglobulin M/G + Remdesivir + Favipiravir + Levofloxacin + N-acetylcysteine | 48,838,326.17    | 0.84              | 58,140,864 |

In comparison, the cost-effectiveness of COVID-19 treatments was measured by calculating the ICER

value. ICER of COVID-19 treatments was primarily located in the 4th Quadrant (South East Quadrant), with the

Favipiravir + Levofloxacin + N-acetylcysteine being the dominant compared to other treatments. Incremental analysis showed that using Favipiravir + Levofloxacin + N-acetylcysteine resulted in the saving of

IDR 161,653.97 to 33,870,916.17 per recovered patient. This indicates that the cost of Favipiravir + Levofloxacin + N-acetylcysteine was comparable to its effectiveness as demonstrated in Figure 1.



**Figure 1.** Incremental Cost Effectiveness Ratio (ICER) of COVID-19 Treatment

*Note: 1st therapy: Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine; 2nd therapy: Favipiravir + Azithromycin + N-acetylcysteine; 3rd therapy: Favipiravir + Levofloxacin + N-acetylcysteine; 4th therapy: Remdesivir + Favipiravir + Levofloxacin + Azithromycin + N-acetylcysteine; 5th therapy: Immunoglobulin M/G + Remdesivir + Favipiravir + Levofloxacin + N-acetylcysteine*

## DISCUSSION

This investigation is the first published cost-effectiveness evaluation of treatment for COVID-19 inpatients in Indonesia, focusing on the healthcare provider perspective. Individuals of all ages, genders, and marital statuses are susceptible to contracting COVID-19. Nevertheless, patients aged 60 years or older and those with pre-existing medical conditions, such as cardiovascular disease, diabetes, obesity, chronic lung disease, chronic kidney disease, and smoking, are at a higher risk of developing severe infection and related complications<sup>12</sup>. According to a previous study,<sup>13</sup> the prevalence of COVID-19 in Indonesia was dominated by women, which is consistent with the findings of this study. However, another

study<sup>14</sup> reported that a higher prevalence of symptomatic COVID-19 was observed in men, with smoking and alcohol consumption contributing to the higher rate. The association between educational attainment and the risk of severe COVID-19 symptoms remains ambiguous. Less educated populations and disadvantaged socioeconomic backgrounds may be more susceptible to developing severe COVID-19 symptoms due to inadequate housing conditions, overcrowding, and low-paid essential occupations that make adherence to social distancing more difficult.<sup>15,16</sup>

In particular, most patients or 86.28% had a length of stay (LOS) ranging from 7 to 14 days. The LOS is a vital efficiency indicator in the payment system and hospital management. The decrease in inpatient days culminated in a lower risk of

infection, improved quality of treatment, and increased hospital profit with more efficient bed management<sup>17,18</sup>. Meanwhile,<sup>19</sup> a previous study claimed that from a medical point of view, the longer duration of treatment indicates poor medical performance because the patient must receive a longer recovery. Based on the interview with the head of the hospital pharmacy, the hospital had no COVID-19 clinical pathway to standardize the health provision, including therapy, LOS, medical service, and supporting examination. This problem caused the difference in the treatment and supporting examination among the doctors.

Based on the guideline in Indonesia, the therapy was used with several options for COVID-19 combination treatment, including antiviral, antibiotic, and mucolytic.<sup>11,20</sup> An antiviral drug approved and utilized globally as a COVID-19 treatment, including in Indonesia, is favipiravir.<sup>21</sup> It is classified as a guanine analog antiviral agent and is highly effective in obstructing the RNA-dependent polymerase of RNA viruses, which encompasses influenza, Ebola, yellow fever, yellow fever, chikungunya, norovirus, and enterovirus. Moreover, a recent study has established its potential in combating SARS-CoV-2.<sup>22</sup>

Remdesivir is a prodrug of a synthetic adenosine analog and its mechanism of action involves binding to the viral RNA-dependent polymerase, thereby hindering viral replication by causing premature termination of RNA transcription.<sup>23</sup> A previous study revealed that Remdesivir demonstrated in-vivo and in-vitro activity against SARS-CoV-2. Moreover, its efficacy has been established in several clinical trials wherein it was compared to the standard of care and proved beneficial in treating COVID-19.<sup>24</sup> It became the first drug to receive emergency use authorization from the US

Food and Drug Administration (FDA) for treating hospitalized COVID-19 patients.<sup>25</sup> In Indonesia, Remdesivir has been approved to treat severe hospitalized COVID-19 patients<sup>11</sup>.

According to the initial treatment in Indonesia<sup>11</sup>, antibiotics, such as Azithromycin and Levofloxacin, can be added when there is a suspected bacterial co-infection. These antibiotics were previously listed as a combination for handling moderate to severe degrees of COVID-19. In this study, Azithromycin and Levofloxacin were used by doctors as support therapy in patients with suspected bacterial life-threatening organ dysfunction sepsis.<sup>26</sup>

N-acetylcysteine has been used in clinical practice to treat critically ill septic patients, paracetamol intoxication, and as a mucolytic. More recently, it has been repurposed for COVID-19 patients.<sup>27</sup> Based on pathological studies, it was found that abundant mucus secretion, formation of a hyaline membrane, and interstitial fibrous exudation may be essential characteristics of COVID-19 pathological target of drug therapy, namely as a mucolytic agent. Another pathology review explained that excessive immune activation, cytokine storm, and inflammation in the disease culminated in imbalanced redox homeostasis. Therefore, antioxidants, free radical scavenging, and anti-inflammatory actions of N-acetyl cysteine (NAC) might be the reason for its use as an adjuvant COVID-19 treatment.<sup>28,29</sup>

The lowest ACER value indicates the most cost-effective treatment and the result depicted that the combination of Favipiravir + Levofloxacin + N-acetylcysteine with the value IDR 15,596,973 was the most cost-effective. The ICERs can be analyzed to determine the additional costs per unit of effectiveness and to recommend alternative interventions based on funding availability.<sup>31</sup> It was

evaluated by using the criteria on cost-effectiveness of global health according to the threshold of Gross Domestic Product (GDP) per capita: (i) highly cost-effective (less than one GDP per capita); (ii) cost-effective (between one to three times GDP per capita); and (iii) cost-ineffective (more than 3 times GDP per capita).<sup>30</sup> Considering the GDP per capita in Indonesia of US\$ 3,892.54 (IDR 5,788,206,980), the result confirmed that Favipiravir + Levofloxacin + N-acetylcysteine was the highly cost-effective and also considered dominant compared to the other four treatments as shown in Figure 1. This investigation also agrees with another pharmacoeconomic study in Russia that selected Favipiravir as the most effective medication over Remdesivir and Umifenovir.<sup>32</sup> Another study also discovered that the use of Favipiravir therapy culminated in reduced expenses compared to standard of care (SC) and demonstrated a 4% higher likelihood of being discharged alive.<sup>33</sup>

Moreover, this study found that the use of Remdesivir combination was more costly. This finding is consistent with a previous study<sup>34</sup> in which all strategies involving the use of Remdesivir were less effective and more expensive than SC as well as dexamethasone in treating moderate to severe cases of COVID-19 in Canada. However, another study<sup>35</sup> demonstrated that the ICER of 5-day Remdesivir treatment compared to standard of care (SC) was substantially lower than the GDP per capita threshold and was positively considered for treating severe COVID-19 patients in China.

Presently, the experience with the use of intravenous Immunoglobulin M/G (IVIG) in the treatment of SARS-CoV-2 infection is minimal. Based on a previous study, the rationale for its use is the modulation of inflammation.<sup>36</sup> The anti-inflammatory mechanisms of IVIG can reduce the inflammatory response in severe SARS-CoV-2 infection, including autoreactive antibodies that bind

cytokines.<sup>37</sup> IVIG therapy is also one of the alternative therapies, notably in the severe case of COVID-19.<sup>11,38</sup>

Several limitations need to be considered when interpreting this study, first, the rapidly evolving nature of the COVID-19 pandemic means that the information used is constantly changing and may be less accurate than the evidence obtained through real-world studies. Consequently, this analysis might have oversimplified the COVID-19 patient experience and the associated long-term burden. This study was also restricted by the cost-effectiveness analysis of individual treatments, which fails to explicitly consider the potential benefits of emerging combination treatments for inpatient care.

The COVID-19 pandemic had significant health and economic consequences worldwide, and treatments that can reduce its burden are desperately needed.<sup>34</sup> Currently, the treatment landscape is progressing at an unprecedented pace, with over 744 therapeutics being tested in 2879 active clinical trials.<sup>39</sup> This study provides fundamental data on the predicted cost-effectiveness of available and in-development inpatient treatments for COVID-19 in Indonesia. Hopefully, these findings can assist policymakers in developing guidelines for the treatment of COVID-19 that are both effective and cost-efficient for the Indonesian population.

## RECOMMENDATION

The COVID-19 pandemic has drastically burdened the public health, healthcare system, and economy in Indonesia. Effective COVID-19 treatments for hospitalized patients might reduce disease burden and significantly represent good value for the health system and society. This analysis suggests that the combination of Favipiravir + Levofloxacin + N-acetylcysteine is highly cost-effective compared to other treatments. There are

certain limitations associated with this study due to the unavailability of up-to-date information about the rapidly evolving pandemic. These include the newly emerged viral variants, the characteristics of affected patient populations, and changing standards of care. Therefore, additional investigation is needed to examine the influence of vaccination on the cost-effectiveness of COVID-19 treatments, based on real-world data that takes these developments into account.

There are several areas of possible future investigations highlighted in this study. As more treatments for COVID-19 patients become available, and the treatment guidelines are continually developed, future updates to this cost-effectiveness analysis are needed. Moreover, there is a need to assess the cost-effectiveness, including productivity loss such as absenteeism, presenteeism, caregiving, and household contributions, as well as the broader economic impact on non-healthcare sectors, which includes consumption and social services. The clinical pathway of COVID-19 inpatients should also be developed to standardize the therapy LOS, medical procedure, and supporting examinations.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTION

MSR, Y, and DD conceived the idea; MSR and Y conducted the study;

MSR, Y, DD, and MRE analyzed the data. MSR, DD, and MRE developed the article, wrote, prepared the manuscript and made the final version.

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