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Cost-utility analysis for non-small cell lung cancer with epidermal growth factor receptor mutations

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Abstract

Introduction: Lung cancer remains a leading cause of death worldwide, with non-small cell lung cancer (NSCLC) carrying the highest incidence among lung cancer types, particularly in patients with epidermal growth factor receptor (EGFR) mutations. The first-line therapy for NSCLC lung cancer patients with EGFR mutations typically involves the tyrosine kinase inhibitor (TKI) group.

Objective: The study aimed to compare the cost utility of the two TKI groups (afatinib and erlotinib) for NSCLC patients with EGFR mutations.

Method: This pharmacoeconomic study was conducted using the Cost Utility Analysis (CUA) method from the patient's perspective. The study included 33 patients receiving afatinib and 12 patients receiving erlotinib, conducted in 2022-2023 at Kariadi Hospital, Semarang, and Prof. Dr. Margono Soekarjo Hospital, Purwokerto. Therapeutic outcomes were measured using Quality Adjusted Life Year (QALY), and cost components included actual costs and estimated costs based on clinical pathways. CUA was presented in the form of an Incremental Cost Effectiveness Ratio (ICER).

Results: The cost of afatinib was greater than that of erlotinib (IDR 174,395,847 vs. IDR 138,672,688). The quality of life of afatinib was better than that of erlotinib (0.397 vs. 0.161, *p*-value 0.016). The ICER of afatinib was IDR 151,369,318 per QALY when compared to erlotinib.

Conclusion: This study demonstrates that afatinib is a cost-effective treatment option for NSCLC patients with EGFR mutations.

Keywords: Afatinib, EGFR, erlotinib, ICER, mutation

1. Introduction

The increasing number of deaths from lung cancer is a growing concern globally. According to the World Health Organization (WHO), lung cancer was responsible for 2,206,671 deaths in 2020, accounting for 11.4% of all cancer-related fatalities (Lukeman, 1976; Globocan, 2020). In the United States, lung cancer deaths caused 1,796,144 deaths, or 18% of the total number of cancer cases, while in Asia, deaths caused by lung cancer reached 1,315,136 cases, or 19.2% of the total number of cancer cases (Globocan, 2020; Globocan Asia, 2021). Meanwhile, in Indonesia, lung cancer was the leading cause of cancer-related deaths, with 11.4% of the country's cancer cases in 2020 and a male-to-female ratio of 13:1 (Joseph & Rotty, 2020; Sutnick & Gunawan, 1982).

The incidence of lung cancer cases with the type Non-Small Cell Lung Cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutations varies (Cagle *et al*., 2013). The proportion of NSCLC cases in Indonesia is considered relatively high, with a proportion of more than 70% of the total lung cancer cases (Robot *et al.*, 2021). This type of cancer often leads to chronic symptoms such as prolonged coughing, with eventual mortality due to lung failure. In addition to the impact of physical conditions, other impacts include more complex medical therapy than other types.

Effective therapy for lung cancer patients with EGFR mutations can improve survival rates and reduce disease severity. First-line therapy for NSCLC lung cancer patients with EGFR mutations is the tyrosine kinase inhibitor (TKI) group, such as erlotinib, gefitinib, and afatinib (de Man *et al*., 2019; Novello *et al*., 2016). These three drugs are used to treat EGFR-positive mutations, including exon 19 and exon 21 L858R deletions (Maemondo *et al*., 2010). Among them, afatinib and erlotinib are the most commonly used tyrosine kinase inhibitors from the TKI group because they are more effective than other chemotherapy drugs (Nasrulsyah *et al*., 2020; Yang *et al*., 2017). Afatinib is also considered superior because it blocks the formation of protein kinases through ligands in cancer cells, preventing the early stages of cancer cell formation (Kim *et al*., 2021). Clinical data showed that for 467 NSCLC patients with positive EGFR mutations, afatinib provided a longer Progression-Free Survival (PFS) (19.1 months) compared to erlotinib (7.1 months) and gefitinib (14 months) (Brueckl *et al*., 2018; Kim *et al*., 2021; F. Wulandari *et al*., 2021; Yang *et al*., 2017).

The presence of mutations in lung cancer patients not only complicates treatment but also increases costs. The effectiveness and efficiency of the treatment are a growing concern for the government, especially in the implementation of the National Health Insurance (JKN) program (Hadiningsih, 2015). Previous research indicates that the average cost for a lung cancer patient undergoing first-line chemotherapy is IDR 14,561,930 (Wulandari *et al*., 2019). Moreover, the cost of lung cancer is considered relatively expensive compared to other cancers when viewed from the comparison of the cost/Progression-Free Survival (PFS) ratio. The cost of erlotinib is IDR 1,693,139/month, gefitinib is IDR 1,227,323/month, and afatinib is IDR 2,429,366/month. Of these, gefitinib therapy is the most economical TKI, followed by erlotinib and afatinib. However, when compared to standard therapy, the average cost of the TKI group is more expensive (IDR 12,000,000) than the cost of standard therapy (IDR 8,869,645) (Nurhayati *et al*., 2021; Wulandari *et al*., 2019).

Given these concerns, this study aims to compare the two TKI treatments (afatinib with erlotinib) to assess the cost-utility of these therapies. This comparison is crucial to guide Health Technology Assessment (HTA) activities in Indonesia in lung cancer patients with EGFR mutations.

2. Methods

2.1. Description of materials and sample collection techniques

This pharmacoeconomic study was conducted using the Cost Utility Analysis (CUA) from the patient perspective, focusing on NSCLC lung cancer patients with EGFR mutations. This study was conducted on patients receiving TKI therapy between 2022 and 2023 at Kariadi General Hospital Semarang and Prof. Dr. Margono Soekarjo General Hospital Purwokerto. Ethical approval was

granted by the Health Research Ethics Commission of Universitas Muhammadiyah Purwokerto with the ethical eligibility number KEPK/UMP/101/I/2023.

Purposive sampling was carried out to select patients who met the following inclusion criteria: patients diagnosed with NSCLC lung cancer had EGFR mutations, received TKI therapy, and had received at least three therapy sessions. The exclusion criteria in this study were patients with incomplete medical record data and patients who did not complete treatment during the study period. The number of samples taken according to the inclusion-exclusion criteria was 45 patients: 33 patients receiving afatinib therapy and 12 patients receiving erlotinib therapy.

2.2. Research process description

Patient characteristics, such as gender, age, education, occupation, and health insurance, were collected from patient medical records. In comparison, quality of life data was obtained from interviews with patients using EQ-5D-5L (EuroQol 5 Dimensions 5 Levels), which has been standardized in Indonesia. The five dimensions measured in the survey were mobility, self-care, daily activities, pain/discomfort, and anxiety/depression, with the level of statements reported by the patients themselves. The responses are classified into five levels: no difficulty, a little difficulty, quite a bit of difficulty, very difficult, and unable. The results of quality-of-life data were utilities calculated in the Indonesian value set (Hamida *et al*., 2019).

The cost data collected in this study included direct medical, direct non-medical, and indirect cost data. Direct medical costs were obtained from patient billing at the hospital, covering drugs and medical devices, laboratories, accommodation, and doctor visits. The cost data were then grouped into costs when patients underwent surgery, targeted therapy, and radiotherapy (Restyana & Admaja, 2019). Direct non-medical cost data included parking, food, and transportation costs collected through interviews. Indirect costs, including productivity loss, were also collected through interviews. The three types of cost data were classified as actual costs, where this data describes the real costs incurred during therapy. Furthermore, the actual cost data obtained from the hospital and the patient were weighted by the clinical pathway obtained from The National Comprehensive Cancer Network (NCCN) to calculate the unit cost required by patients when diagnosed with lung cancer. Based on the 2020 NCCN guidelines, patients are recommended to undergo surgery once, target therapy six times, and radiotherapy 30 times (Ettinger *et al*., 2021).

2.3. Statistical analysis

The statistical analyses used in this study were chi-square, independent sample t-test, and cost-effectiveness. Chi-square analysis was used to test the difference between the characteristics of the afatinib and erlotinib groups. Independent sample t-test analysis was utilized to test the difference in numerical data on the age and utility variables for the use of afatinib and gefitinib therapies. Cost-effectiveness analysis was calculated using the Incremental Cost Effectiveness Ratio (ICER) (Ardhila *et al*., 2024), whose value was compared to the Willingness to Pay (WTP) in Indonesia. The determination of the WTP value is based on 3 times the Gross Domestic Product (GDP) per capita in 2021, which is 186.6 million/utility index (Atikasari *et al*., 2023).

3. Result and discussion

3.1. Characteristics patient

The demographic characteristics of NSCLC lung cancer patients with EGFR mutations in afatinib and erlotinib groups show similarities in terms of gender, age, education level, occupation, and health insurance categories used (p-value > 0.05) (**Table 1**). Most patients were female (24 people (53.33%)), which corroborates findings by Fujiwara *et al*. (2018), who report that NSCLC is more prevalent among women. The estrogen hormone might influence lung cell differentiation and EGFR activation, contributing to this higher incidence in women (Fujiwara *et al*., 2018; Hsu *et al*., 2017).

The average age of lung cancer patients with EGFR mutations was 52 years, classifying them as older adults. It is in line with previous studies suggesting that older adults are vulnerable to being the main factor (Fujiwara *et al*., 2018; Oktaviyanti, 2015). Another theory also states that age affects the occurrence of oncogenesis, so increasing age affects genetic changes that have an impact on the decline in stem cell function. In normal individuals, stem cells can act as a barrier to tumor growth by creating an environment that is not conducive to gene mutations. Age-related declines in stem cell function may increase the risk of genetic mutations, including EGFR mutations, due to reduced tumor-suppressive barriers (Tezel *et al*., 2017).

In this study, the highest level of patient education was at the high school level, the majority of patient education was in high school (23 patients (250.11%)). Based on research findings by Sulviana and Kurniasari (2021), 140 out of 216 cancer patients are in high school. While higher education levels are not directly linked to cancer risk, unhealthy lifestyles can elevate the risk regardless of education level (Balatif & Sukma, 2021). Meanwhile, the majority of lung cancer patients with EGFR mutations are private employees, most were private employees 15 (33.3%).

According to research by Pritami *et al*. (2022), the type of work can increase the risk of lung cancer. Exposure to air pollution and chemicals from the work environment can trigger lung cancer. However, these factors are not found to significantly contribute to EGFR mutation-related NSCLC (Putriani *et al*., 2019). Meanwhile, health insurance does not affect therapy coverage; it affects the patient's source of funds.

Table 1. Respondent characteristics

Variable	Afatinib (N=33)		Erlotinib (N=12)		Total (N=45)		*P*-value
	N	%	N	%	N	%	
Gender							
Female	16	48.5	8	66.7	24	53.33	0.679
Male	17	51.5	4	33.3	21	46.67	
Age							
Mean (SD)	52.52 (11.97)		53.3 (12.37)		52.73 (11,94)		0.842
Median (min: max)	52 (21:71)		55 (21:70)		54 (21:71)		
Education							
Bachelor	6	18.2	4	33.3	10	22.22	0.691
Senior High School	20	60.6	3	25	23	50.11	
Junior High School	4	12.1	3	25	7	15.56	
Elementary School	3	9.1	2	16.7	5	11.11	
Occupation							
Work	21	63.6	11	97.67	32	71.1	0.377
Not working	12	36.4	1	8.3	13	28.9	
Health assurance							-
BPJS	31	93.90	12	100	43	95.56	
Non-BPJS	2	6.1	-		2	4.44	

3.2 Quality of live of patients

The quality of life of patients in both therapy groups illustrated different utility values (**Table 2**). The quality of life of the afatinib group was higher than that of gefitinib (0.397 vs. 0.161, *p*-value 0.016). However, the VAS value was only found in the afatinib group (77.667 ± 4.169). Dwilovianita *et al*. (2022) reported that 85% of cancer patients experienced pain or discomfort, while 36.7% had mild anxiety, 23.3% had moderate anxiety, and 46% had severe anxiety. This pain is attributed to the effects of the drug or from the cancer itself. Increased anxiety occurs due to patients' fear of their future as they face lung cancer. Patients feel anxious because of medical procedures, such as surgery, chemotherapy, and target therapy or hormone therapy, especially when these treatments are prolonged (Dwilovianita *et al*., 2022).

Tabel 2. Quality-of-life

Dimensions	Levels	Afatinib (n=23)	Erlotinib (n=4)	Total (n=27)
Mobility	No problem	4 (17.4%)	0 (0%)	4 (14.8%)
	There is a problem	19 (82.6%)	4 (100%)	23 (85.2%)
Self-care	No problem	7 (30.4%)	0 (0%)	7 (25.9%
	There is a problem	16 (69.6%)	4 (100%)	20 (74.1%)

Dimensions	Levels	Afatinib (n=23)	Erlotinib (n=4)	Total (n=27)
Daily activity	No problem	1 (4.3%)	0 (0%)	1 (3.7%)
	There is a problem	22 (95.7)	4 (100%)	26 (96.3)
Pain/discomfort	No problem	0 (0%)	0 (0%)	0 (0%)
	There is a problem	23 (100%)	4 (100%)	27 (100%)
Anxiety/depression	No problem	0 (0%)	0 (0%)	0 (0%)
	There is a problem	23 (100%)	4 (100%)	27 (100%)
Utility	Mean ± SD	0.397 ± 0.172	0.161 ± 0.145	*p-Value* 0.016
VAS	Mean ± SD	77.667 ± 4.169	-	-

3.3 Cost analysis

The actual total cost required for NSCLC lung cancer patients with EGFR mutations to maintain treatment using afatinib was higher than for erlotinib patients (IDR 36,460,407 ± 18,686,717 vs. IDR 34,052,431 ± 15,944,215). It was primarily due to the direct medical costs of NSCLC lung cancer patients with EGFR mutations using afatinib were higher than those of erlotinib (IDR 35,819,553 ± 18,028,849 vs. IDR 33,560,764 ± 15,440,757). However, the direct non-medical costs of afatinib therapy were lower than those of erlotinib (IDR 137,521 ± 152,436 vs. IDR 217,500 ± 130,032). Additionally, the indirect costs of therapy with afatinib were higher than those of erlotinib (IDR 503,333 ± 505,432 vs. IDR 274,167 ± 373,426) (**Table 3**). Patients receiving gefitinib 150 required lower costs than the afatinib group (IDR 36,460,407 ± IDR 18,686,717 vs. IDR 34,052,431 ± IDR 15,944,215). It aligns with previous studies indicating that additional costs for afatinib therapy are higher ($9745) than those of gefitinib and erlotinib (Kim *et al*., 2021). Other factors determining the difference in total costs are the frequency of visits to the hospital and the existence of supporting examinations, which contribute to administrative and service costs (Nurhayati *et al*., 2021).

3.3. Incremental Cost Effectiveness Ratio (ICER)

A cost analysis based on clinical pathways discovered that the total cost of afatinib therapy was higher than that of erlotinib (IDR 174,395,847 vs. IDR 138,672,688) (**Table 4**). The Incremental Cost-Effectiveness Ratio (ICER) for afatinib administration was calculated to be IDR 151,369,318/ Quality-Adjusted Life Year (QALY) when compared with erlotinib. This study was consistent with the study by You *et al*. (2021), who reported that the direct medical costs of afatinib were significantly higher ($35,808) compared to erlotinib ($18,724). Similarly, Gu *et al*. (2019) found that afatinib is more expensive ($43,629), than erlotinib ($40,811).

Table 3. Cost analysis

Cost Component	Afatinib		Erlotinib		All Patients	
	Mean (IDR)	SD (IDR)	Mean (IDR)	SD (IDR)	Mean (IDR)	SD (IDR)
Surgery		**N=6**		**N=5**		**N=11**
Pharmacy	2,624,344	1,112,090	3,567,624	2,321,376	3,095,984	1,716,733
Laboratories	2,640,017	1,452,727	2,562,360	1,955,647	2,601,189	1,704,187
Accommodation	5,200,000	3,108,054	6,130,000	4,969,859	5,665,000	4,038,957
Visited the doctor	3,040,000	753,870	2,388,000	2,006,370	2,714,000	1,380,120
Administration	31,000	5,292	35,600	7,603	33,300	6,448
Medical treatment	3,831,083	2,545,174	5,799,100	970,458	4,815,092	1,757,816
Care treatment	842,000	199,721	694,600	578,167	768,300	388,944
Radiology	2,725,583	1,798,443	2,161,700	1,382,518	2,443,642	1,590,481
Total cost	20,934,027	10,975,371	23,338,984	14,191,998	22,136,506	12,583,685
Targeted therapy		**N=33**		**N=12**		**N=42**
Registration	15,152	14,169	26,250	2,261	20,701	8,215
Pharmacy	1,771,302	2,665,498	222,947	90,937	997,125	1,378,218
Laboratories	119,367	50,965	91,333	4,677	105,350	27,821
Targeted therapy	10,545,891	2,720,162	8,113,333	9,847	9,329,612	1,365,005
Radiology	1,149,470	786,405	501,125	555,242	825,298	670,824
Total cost	13,601,182	6,237,199	8,954,988	662,964	11,278,085	3,450,082
Radiotherapy		**N=18**		**N=12**		**N=30**
Registration	17,273	11,531	26,250	2,261	21,762	6,896
Laboratories	94,985	5,803	89,750	4,961	92,367	5,382
Radiotherapy	736,364	93,602	825,000	45,227	780,682	69,415
Radiology (CT-Scan)	435,722	705,343	325,792	533,346	380,757	619,345
Total cost	1,284,344	816,279	1,266,792	585,795	1,275,568	701,037
Total direct medical cost	**35,819,553**	**18,028,849**	**33,560,764**	**15,440,757**	**34,690,158**	**16,734,803**
Direct non-medical cost		**N=23**		**N=4**		**N=27**
Parking	4,913	5,239	5.000	0	4,957	2,620
Food	38,478	13,180	67,500	22,174	52,989	17,677
Transportation	94,130	134,017	145,000	107,858	119,565	120,938
Total direct non-medical cost	**137,521**	**152,436**	**217,500**	**130,032**	**177,511**	**141,234**
Indirect cost		**N=23**		**N=4**		**N=27**
Productivity loss	503,333	505,432	274,167	373,426	388,750	439,429
Total indirect cost	**503,333**	**505,432**	**274,167**	**373,426**	**388,750**	**439,429**
TOTAL COST	**36,460,407**	**18,686,717**	**34,052,431**	**15,944,215**	**35,256,149**	**17,315,466**

This study demonstrated that the use of afatinib for NSCLC lung cancer patients with EGFR mutations was a cost-effective strategy when compared to erlotinib. Although the cost of afatinib was higher than erlotinib, patients receiving afatinib reported a better quality of life than those treated with erlotinib. The determination of the WTP value is based on 3 times the Gross Domestic Product (GDP) per capita in 2021, which is 186.6 million/utility index (Atikasari *et al*., 2023). This finding aligns with previous research indicating that afatinib therapy provides higher effectiveness and QALY values than erlotinib (Kim *et al*., 2021; Zhu *et al.*, 2018). Moreover, afatinib is considered a cost-

saving strategy compared with erlotinib and gefitinib for EGFR mutation-positive NSCLC patients (Kim *et al.*, 2021; Zhu *et al*., 2018).

Tabel 4. Cost analysis based on clinical pathway

Treatment	Afatinib				Erlotinib				ICER
	Cost (IDR)	Quantity	Total (IDR)	QALYs	Cost (IDR)	Quantity	Total (IDR)	QALYs	
Surgery	20,934,027	1	20,934,027		23,338,984	1	23,338,984		
Targeted therapy	13,601,182	6	81,607,092		8,954,988	6	53,729,928		
Radiotherapy	1,284,344	30	38,530,320		1,266,792	30	38,003,760		
Direct-nonmedical cost	137,521	52	7,151,092		217,500	48	10,440,000		
Non-direct cost	503,333	52	26,173,316		274,167	48	13,160,016		
Total			**174,395,847**	**0.397**			**138,672,688**	**0.161**	**151,369,318**

One of the limitations of this study was the lack of data on the toxicity profiles and side effects of each treatment, which could affect the results of the patient's quality of life. Further research is needed, including the assessment of Drug Related Problems (DRP), as cancer patients often experience more side effects. Data on quality-of-life subjects were limited due to the challenges in directly interviewing patients. Future studies could involve other patients in similar conditions to increase the number of respondents. VAS scores were missing for one group due to differences in enumerator perceptions during data collection; this issue could be mitigated by standardizing data collection. Another limitation was the small sample size; therefore, further research should include a larger and more diverse population across multiple research locations in Indonesia. Comparative studies on other TKI groups, such as gefitinib, could also provide a more comprehensive cost-utility profile of TKI group therapies.

5. Conclusion

The administration of afatinib is considered to be more cost-effective than erlotinib for NSCLC lung cancer patients with EGFR mutations.

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