RESEARCH ARTICLE

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Do Generic *EGFR-TKIs* Perform as Well as Innovators? Real-World Evidence from Gefitinib-Treated EGFR-Mutated NSCLC in Indonesia

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Abstract

Background: Gefitinib is standard first-line therapy for $EGFR$-mutated non-small cell lung cancer (NSCLC). Following Indonesia's 2020 transition to generic gefitinib in national procurement, real-world comparative data remain limited. This study compared clinical outcomes between innovator and generic gefitinib in Indonesian referral hospitals. **Methods:** We conducted a retrospective cohort study of adults with *EGFR*-mutated NSCLC receiving first-line innovator or generic gefitinib between 2019–2022 at national cancer center and national respiratory center. The effectiveness was evaluated using progression-free survival (PFS) estimated by Kaplan–Meier and compared with the log-rank test; hazard ratios (HRs) were derived from Cox regression. Adverse events (AEs) were abstracted from patients' medical records based on physicians' documentation in the clinical progress notes and analyzed using Mann-Whitney tests. Multivariable analyses were performed to evaluate the association between gefitinib type (generic vs. innovator) and clinical outcomes while adjusting for potential confounders, including demographics, smoking status, comorbidities, disease stage, ECOG performance status, radiotherapy history, COVID-19 history, mutation subtype, and hospital. The follow-up period was 18 months within a 4-year horizon. **Result:** A total of 192 patients met the inclusion criteria (innovator n = 124; generic n = 68). The median PFS was 12.2 months (95% CI, 8.7–15.7) in the innovator group and 16.4 months (95% CI, 13.7–19.1) in the generic group. Although the generic formulation demonstrated a numerically longer median PFS, the difference was not statistically significant (HR = 1.61, 95% CI, 0.98–2.63; p = 0.104). Multivariate analysis showed that no baseline variable was significantly associated with PFS after adjustment. Safety profiles were generally comparable, but dermatologic and gastrointestinal AEs occurred more frequently with the generic formulation, with significantly higher frequencies (rate-adjusted) of diarrhoea, paronychia, and stomatitis (p = 0.002, 0.011, and 0.001, respectively). Other AEs, including dyspepsia, alopecia, neuropathy, and AST/ALT elevation did not differ significantly between groups. **Conclusion:** The generic formulation demonstrated comparable efficacy to the innovator drug in terms of progression-free survival, although a higher incidence of certain mild-to-moderate adverse events was noted. These findings support the therapeutic use of the generic gefitinib with careful monitoring of tolerability.

Keywords: Gefitinib, Generic Drug, Non–Small Cell Lung Cancer, *EGFR* Mutation, Indonesia

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Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths annually. In Indonesia, it has the highest incidence among males compared with other types of cancer, with a rate of 19.4 per 100,000 men, according GLOBOCAN 2022 [1]. Approximately 85% of lung cancer cases are classified as non-small cell lung cancer (NSCLC) [2]. Given the high prevalence of *EGFR* mutations in Indonesia, reported at over 44% [3], tyrosine kinase inhibitors (TKIs) have emerged as a promising treatment option for NSCLC. TKIs function as targeted therapies by directly inhibiting cancer-specific molecules and signaling

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pathways, thereby minimizing the nonspecific toxicities typically associated with conventional chemotherapy [4].

First- and second-generation *EGFR-TKIs* have demonstrated superior overall survival outcomes compared with platinum-based chemotherapy and are widely used as first-line treatments for *EGFR*-mutated NSCLC, particularly in Asian populations [5]. Their role as standard first-line therapy is further supported by recommendations from the National Comprehensive Cancer Network (NCCN) guidelines [6]. Given this advantage, subsequent studies have focused on comparing the effectiveness among different *EGFR-TKIs* to determine the most optimal treatment option. Furthermore, a study conducted in Indonesia showed that gefitinib provided longer progression-free survival (PFS) compared to erlotinib and afatinib [7].

In Indonesia, physicians and pharmacists exhibited satisfactory perception and positive attitudes towards generics [8]. However, a systematic review by Dunne et al. revealed that a strong belief among patients or consumers that lower cost equates to lower quality. Acceptance of generic medicines tends to be higher among consumers with higher education levels, likely due to their greater access to information [9].

However, there has been a notable absence of prior research evaluating the effectiveness and safety of gefitinib following its transition to a generic formulation in Indonesia. Understanding the clinical performance of generic medicines is crucial, as evidence on their real-world effectiveness and safety supports confidence in their use, ensures therapeutic equivalence with the innovator product, and informs rational prescribing. This study was conducted to evaluate the effectiveness and safety of gefitinib, particularly in the context of switching from the innovator to the generic formulation, one of the largest Universal Health Coverage countries, Indonesia, through the National Health Insurance (JKN) program. In Indonesia, the mandatory use of generic medicines, particularly in government healthcare facilities, is regulated by the Ministry of Health Regulation No. HK.02.02/MENKES/068/I/2010, which aims to ensure the availability of safe, quality, and affordable medicines. Therefore, evaluating the real-world effectiveness and safety of generic medicines is important to support confidence in their use within this healthcare system [10].

A prior study by Cheng et al. [11] in China compared innovator and local generic gefitinib and found no significant difference in PFS between the two groups . Referring to that study, similar evaluations of effectiveness and safety are also crucial in Indonesia, especially following the recent policy shift within the JKN program, which now utilizes only the generic version. Since this change directly affects a large number of patients, generating local real-world evidence is essential. Determining whether the generic formulation provides equivalent effectiveness and safety to the innovator is not only crucial for resource optimization but also for ensuring patient safety, maintaining treatment outcomes, and preserving public trust in cancer therapy.

This study aimed to compare the real-world effectiveness and safety of innovator versus generic gefitinib in patients with *EGFR*-mutated NSCLC treated under the Indonesian JKN program.

Materials and Methods

Study Design

This study employed a retrospective cohort design involving patients diagnosed with *EGFR*-mutated NSCLC who received Gefitinib therapy between January 2019 and December 2022 at two national referral hospitals in Indonesia, the Dharmais National Cancer Center and Persahabatan National Respiratory Center hospital. Although gefitinib has been available in Indonesia since 2015, the study period began in 2019 to capture treatment outcomes primarily associated with the innovator product prior to the widespread implementation of generic gefitinib through national procurement starting in 2021.

Patients were followed for 18 months from treatment initiation to assess progression-free survival. The study applied a 4-year time horizon, encompassing the entire period during which eligible patients received gefitinib and were observed for clinical outcomes.

Study Population

Eligible participants were adults aged 18 years or older who had received either innovator or generic gefitinib as first-line therapy under the JKN program for at least three months. This minimum treatment duration was required because tumor response in clinical practice is generally evaluated every three months according to the Response Evaluation Criteria in Solid Tumors (RECIST). Patients who had previously received other tyrosine kinase inhibitors (TKIs) were excluded and for patients who switched between the innovator and generic formulations during treatment, follow-up was censored at the time of switching, and the treatment episode was considered ended without outcome occurrence.

A total of 410 patients received either innovator or generic gefitinib therapy from January 2019 to December 2022. Three patients who previously received a TKI other than gefitinib were excluded from the analysis. Among the remaining 407 patients who received only gefitinib therapy, 202 patients had treatment durations of less than three months and were excluded according to the inclusion criteria. Thus, 205 patients received either innovator or generic gefitinib therapy for at least three months, and ultimately 192 were eligible for analysis: 124 received innovator gefitinib and 68 received the generic formulation.

Data Collection

Clinical data were obtained from electronic and manual medical records, including demographic information (age, gender, smoking history, and family history of cancer), clinical characteristics (disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, and prior radiotherapy or COVID-19 infection), and mutation subtype. Data were obtained from medical records and administrative reports. We compared the effectiveness (PFS), adverse drug reactions, and total therapy costs of patients who

used innovator and generic gefitinib from January 2019 to December 2022 using a retrospective observational cohort design. This study also collected data on adverse events (AEs) associated with gefitinib. The most frequently reported AEs included diarrhoea, dyspepsia, paronychia (nail inflammation), stomatitis, alopecia, neuropathy, and various skin disorders such as rash, dry skin, and pruritus. Alanine aminotransferase increased and aspartate aminotransferase (AST/ALT) increased, and these increases were also documented. AEs were analyzed using two complementary measures: the number of patients who experienced at least one AE to describe the proportion of affected individuals, and the event rate to reflect the number of AEs occurrences relative to total drug exposure [12]. To ensure standardized terminology, AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 28.1, using the preferred terms.

Statistical Analysis

Progression-free survival (PFS) was calculated using the Kaplan-Meier method with results reported as median (min – max). Subjects were censored if they voluntary withdrew from the treatment (dropped out), were lost to follow-up, or remained without disease progression until the end of the observation period [13]. The chi-square and Mann–Whitney tests were employed to evaluate differences in baseline characteristics.

To adjust for potential confounding factors, associated with progression-free survival (PFS), a multivariate Cox proportional hazards regression analysis was performed, including gender, smoking history, family history of cancer, comorbidities, disease stage, ECOG performance status, prior radiotherapy, COVID-19 history, mutation subtype, and hospital type.

All statistical analyses were conducted using SPSS software version 29.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant.

Ethical Approval

The study protocol was reviewed and approved by the Ethics Committees of Persahabatan National Respiratory Referral Hospital (No. 62/KEPK-RSUPP/07/2022) and Dharmais Cancer Center Hospital (No. 201/KEPK/VIII/2022). All procedures were performed in accordance with the ethical standards of the institutional and national research committees.

Results

Patient Characteristics

A total of 410 patients received either innovator or generic gefitinib therapy from January 2019 to December 2022. Three patients who previously received a TKI other than gefitinib were excluded from the analysis. Among the remaining 407 patients who received only gefitinib therapy, 202 patients had treatment durations of less than three months and were excluded according to the inclusion criteria. Thus, 205 patients received either innovator or generic gefitinib therapy for at least three months, and ultimately 192 were eligible for analysis: 124 received innovator gefitinib and 68 received the generic formulation

The mean age was 59.41 (1.93) years in the innovator group and 57.49 (3.0) years in the generic group, with no statistically significant difference (p = 0.266). Females predominated in both groups, accounting for 58.1% and 57.4%, respectively (p = 1.000). Most patients in both cohorts were nonsmokers (76.6%) and had no family history of cancer (83.8%).

Regarding clinical status, the majority of patients (94.7%) had stage IV disease at diagnosis, with similar distributions of ECOG performance status across groups. Approximately one-third of the patients had comorbidities, primarily hypertension and diabetes mellitus, and 11.5% had a history of COVID-19 infection. Prior radiotherapy was reported in 26.6% of patients in the innovator group and 36.7% in the generic group (p = 0.143).

EGFR mutation subtypes were predominantly exon 19 deletion (52.6%) and exon 21 L858R (41.7%), with no significant difference between treatment groups (p = 0.451). Overall, baseline demographic and clinical characteristics were well balanced between the innovator and generic gefitinib groups (Table 1).

Effectiveness (Progression-Free Survival)

The median PFS was 12.2 months (95% CI 8.7–15.7) for innovator gefitinib and 16.4 months (95% CI 13.7–19.1) for generic gefitinib. Despite the numerically longer PFS observed in the generic group, comparison of Kaplan–Meier survival curves using the log-rank (Mantel–Cox) test showed no statistically significant difference in PFS distributions between the two groups ($\chi^2 = 2.636$; p = 0.104) (Table 2).

Cox proportional hazards regression analysis showed that none of the evaluated variables were significantly associated with survival. However, a borderline association with survival was observed for history of COVID-19 infection (p = 0.051) and treatment center (hospital) (p = 0.053), although these did not reach the predefined level of statistical significance (p < 0.05) (Table 3).

All other demographic and clinical variables demonstrated no significant association with survival outcomes. Overall, these results suggest that the generic formulation of gefitinib achieved similar clinical effectiveness compared with the innovator drug in patients with *EGFR*-mutated NSCLC treated under the JKN program (Figure 1).

Adverse Events

AEs were identified from medical records. The most frequently reported AEs included dermatologic, gastrointestinal, and hepatic manifestations. In the dermatologic category, the most common AEs were rash, dry skin, pruritus, and paronychia. Gastrointestinal AEs primarily consisted of diarrhoea, stomatitis, and dyspepsia, while hepatic events included alanine aminotransferase increased and aspartate aminotransferase increased. Peripheral neuropathy and alopecia were also observed in several patients.

The number of patients who experienced diarrhoea was

Table 1. Patients Characteristics

Characteristics	Innovator n=124 No. (%)	Generic n=68 No. (%)	p-value
Age at diagnosis			
Age, mean (SD)	59.41 (1.93)	57.49 (3.0)	0.266
Gender			1.000
Male	52 (41.9)	29 (42.6)	
Female	72 (58.1)	39 (57.4)	
Smoking History			0.648
Never	93 (75.0)	54 (79.4)	
Current/Former/ Passive	31 (25.0)	14 (20.6)	
History of Family Cancer			0.099
No	108 (87.1)	53 (77.9)	
Yes	16 (12.9)	15 (22.1)	
Comorbidities			0.113
No	93 (75.0)	43 (63.0)	
Non-Respiration	22 (17.7)	21 (30.8)	
Respiratory disease	9 (7.3)	4 (5.9)	
Stage			0.070
3	4 (3.2)	6 (8.8)	
4	120 (96.8)	62 (91.2)	
ECOG Performance Status			0.060
0	57 (45.9)	43 (63.2)	
1	49 (39.5)	20 (29.4)	
2	18 (14.6)	5 (7.4)	
Radiotherapy History			0.143
Yes	33 (26.6)	25 (36.7)	
No	91 (73.4)	43 (63.3)	
COVID-19 History			0.336
No	110 (88.7)	57 (83.8)	
Yes	14 (11.3)	11 (16.2)	
EGFR Mutation			0.299
Common	120 (96.8)	68 (100)	
Uncommon	4 (3.2)	0 (0)	
End Status			0.111
Progressive Disease	25 (20.2)	11 (16.2)	
Death	16 (12.9)	4 (5.8)	
Lost to Follow up	23 (18.5)	11 (16.2)	
Stable Disease	60 (48.4)	42 (61.8)	

SD, Standard Deviation; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; *The association is significant ($p < 0.05$)

33 (27%) in the innovator group compared with 31 (46%) in the generic group ($p = 0.008$). Similarly, stomatitis was also more frequently observed in the generic group, with 6 (5%) in the innovator group and 13 (19%) in the generic group ($p = 0.020$). Based on the exposure-adjusted event rate analysis, the rate of diarrhoea was significantly higher in the generic group (13.84 ± 2.79%) compared with the innovator group (5.56 ± 1.25%) ($p = 0.002$). Likewise, the rate of stomatitis was greater among patients receiving the generic drug (5.50 ± 1.79%) than those on the innovator formulation (0.65 ± 0.28%) ($p = 0.001$). In addition, the exposure-adjusted rate of paronychia was also significantly higher in the generic group (10.84 ± 2.31%) compared with the innovator group (4.25 ± 0.95%) ($p = 0.011$).

These findings suggested that while the overall safety profiles of the two formulations are were largely similar, the generic formulation may be associated with a higher frequency of certain adverse events affecting the gastrointestinal system and skin appendages.

Table 2 Mean and Median of Progression-Free Survival (PFS)

Variable	Gefitinib Innovator n = 124	Gefitinib Generic n = 68	
Mean PFS	12.9 + 1.1	14.5 + 1.3	
Median PFS	12.2 (8.7- 15.7)	16.4 (13.7-19.1)	
Overall Comparisons			
	Chi-Square	df	p-value
Log Rank (Mantel-Cox)	2.636	1	0.104

Test of equality of survival distributions for the different levels of Gefitinib.

Table 3. Cox Regression Analysis of Factors Associated with Treatment Outcome

Variable	p-value	Statistical significance
Gender	0.643	Not statistically significant
Smoking history	0.420	Not statistically significant
Family cancer history	0.407	Not statistically significant
Comorbidity	0.105	Not statistically significant
Cancer stage	0.199	Not statistically significant
ECOG performance status	0.487	Not statistically significant
Age category	0.860	Not statistically significant
History of radiotherapy	0.875	Not statistically significant
History of COVID-19	0.051	Not statistically significant
EGFR mutation type	0.999	Not statistically significant
Hospital	0.053	Not statistically significant

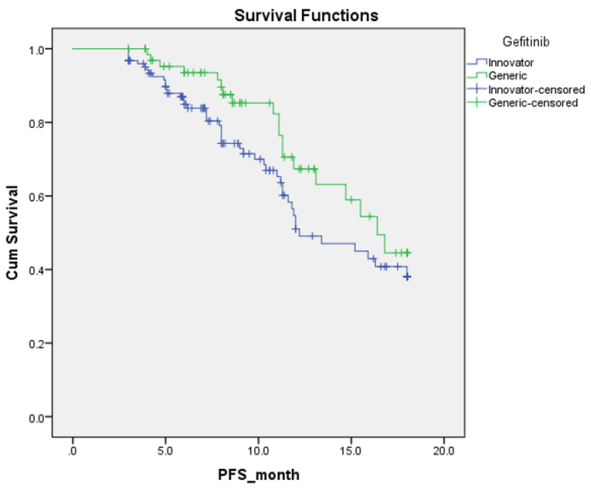

Figure 1. Kaplan–Meier Curves of Progression-Free Survival by Treatment Group

Table 4. Patients Experiencing Adverse Events

Adverse Events	Innovator (n=124)		Generic (n=68)		P-value
	n	%	n	%	
Gastrointestinal Disorders					
Diarrhoea	33	27%	31	46%	0.008*
Dyspepsia	48	39%	30	44%	0.466
Stomatitis	6	5%	13	19%	0.020*
Skin and subcutaneous tissue disorders					
Rash	58	47%	39	57%	0.161
Paronychia	26	21%	22	32%	0.081
Alopecia	2	2%	3	4%	0.348
Nervous system disorders					
Neuropathy	4	3%	4	6%	0.547
Hepatobiliary disorders					
AST/ALT elevation	6	5%	5	7%	0.743

*The association is significant ($p < 0.05$)

Table 5. Exposure-Adjusted Events Rate (number of AE occurrences relative to total drug exposure)

Adverse Events	Innovator		Generic		p-value
	Mean (%)	Deviation	Mean (%)	Deviation	
Gastrointestinal Disorders					
Diarrhoea	5.56	1.250	13.84	2.79	0.002*
Dyspepsia	8.85	1.515	14.82	2.946	0.257
Stomatitis	0.65	0.282	5.50	1.787	0.001*
Skin and subcutaneous tissue disorders					
Rash	11.06	1.542	16.09	2.414	0.058
Paronychia	4.25	0.954	10.84	2.310	0.011*
Alopecia	0.19	0.131	0.53	0.316	0.247
Nervous system disorders					
Neuropathy	0.64	0.270	0.94	0.481	0.485
Hepatobiliary disorders					
AST/ALT elevation	0.77	0.457	0.46	0.231	0.415

*The association is significant ($p < 0.05$)

(Table 4 and 5).

Discussion

In recent years, gefitinib, as one of the TKIs, has been a dependable oral chemotherapy agent for NSCLC with mutant *EGFR*. Its targeted mechanism restores specific molecular signaling pathways and causes fewer adverse drug reactions. Donowati et al. [5] through their systematic review, identified gefitinib as the most frequently used first-generation TKI in real-world studies involving Asian populations, indicating that gefitinib is widely used in clinical practice across Asia.

Since 2015, gefitinib has been used in the treatment of under the JKN program and has been shown to improve PFS [7, 14]. For the first time, the innovator gefitinib was replaced with generic version through the national e-catalogue procurement mechanism in 2020. Only one generic product won the procurement competition and was subsequently adopted nationwide. However, no previous studies have evaluated the effectiveness and safety of this change in Indonesia, as its implementation began only in mid-2021.

Before this study, laboratory testing had been conducted to evaluate the quality of the generic formulation in comparison to the innovator standard. The results showed that the generic product met the acceptable range for weight and content uniformity, as well as dissolution profiles, according to the standards registered with the BPOM, the Indonesian National Agency for Drug And Food Control. However, the dissolution profiles of the generic and innovator products were found not to be identical [15].

Baseline characteristics were collected to determine whether differences in outcomes were influenced by the drug or by other clinical factors. These included age, gender, smoking history, radiotherapy history, COVID-19 infection history, ECOG performance status, mutation subtype, family cancer history, comorbidities, cancer stage, and outcomes at the end of observation. All observed baseline characteristics showed no statistically

significant differences between the innovator and generic groups (Table 1). The number of female patients was higher that of male patients, consistent with research by Syahruddin et al. [17], which showed that women have a higher *EGFR* mutation rate [3]. Jiang et al. [16] in Taiwan also included radiotherapy history as a baseline characteristic to assess its potential impact on therapeutic outcomes . In contrast, Syahruddin et al. [17] reported that history of radiotherapy did not significantly influence the effectiveness of gefitinib . We also included a history of COVID-19 infection as a baseline variable since the treatment period overlapped with the pandemic, which might have affected adherence or clinical condition.

Although most baseline characteristics were statistically similar between groups, ECOG performance status showed a near-significant difference ($p = 0.060$), with a higher proportion of patients having an ECOG score of 2 in the innovator group. This imbalance may have influenced treatment outcomes. Meyers et al. [19] found that NSCLC patients with an ECOG score of 2 or higher had a shorter median overall survival compared with those scoring 0–1. Other studies have confirmed that a poorer performance status correlates with less favorable therapeutic outcomes, including among patients receiving immunotherapy [18, 19]. Therefore, assessing performance status before therapy initiation remains crucial for predicting response and optimizing treatment planning.

This study found that none of the evaluated demographic and clinical variables were independently associated with survival based on Cox proportional hazards regression analysis. Although history of COVID-19 infection and treatment center approached statistical significance, these factors did not meet the conventional threshold, suggesting that their influence on survival may be limited or confounded by other unmeasured variables. The lack of significant associations may be explained by a relatively homogeneous study population, limited sample size, or the predominance of targeted therapy, which could attenuate the prognostic impact of baseline characteristics. Further studies with larger cohorts, longer follow-up, and inclusion of treatment response–related variables are warranted to better clarify determinants of survival in this patient population.

In this study, prior thoracic radiotherapy was not significantly associated with progression-free survival. This finding is inconsistent with previous reports suggesting that prior thoracic radiotherapy may alter the pulmonary microenvironment and affect tissue sensitivity to *EGFR-TKI* therapy [20]. Radiation-induced fibrosis, vascular damage, and altered receptor expression have been proposed as potential mechanisms leading to reduced drug penetration and pharmacodynamic changes. However, in the present study, history of radiotherapy was not significantly associated with survival in the Cox regression analysis, indicating that its impact may be less pronounced in this real-world cohort [20, 21].

Other variables, including ECOG performance status, age, and smoking history, did not show significant associations in this cohort, despite being identified as predictors in prior research [22]. Interestingly, the *EGFR* mutation subtype was also not a significant predictor, although prior evidence suggests that exon 19 deletion and L858R mutations may exhibit differential sensitivity to gefitinib [22]. This may be related to the limited number of patients in specific subgroups within this study. Overall, these findings suggest that baseline demographic and clinical characteristics did not independently influence survival outcomes in this Indonesian real-world cohort.

A previous prospective study evaluating the effectiveness and safety of generic gefitinib was conducted by Cheng et al. in China (2021) with 227 patients from four hospitals [11]. The generic product evaluated was a domestically formulated from China. They found no significant difference in survival outcomes between the innovator and generic groups, and survival data were estimated using the Kaplan–Meier method.

Although patients receiving generic gefitinib demonstrated longer mean and median PFS compared with those receiving the innovator formulation, the absence of statistical significance in the log-rank test indicates that the overall PFS distributions were comparable throughout the follow-up period. The log-rank test evaluates differences across the entire Kaplan–Meier survival curves rather than isolated summary measures, suggesting that the observed numerical differences in mean and median PFS did not reflect a consistent separation of survival patterns over time. Furthermore, censoring and limited follow-up may have influenced the estimation of mean survival time, potentially reducing the power to detect modest differences. Taken together, these findings support comparable PFS outcomes between innovator and generic gefitinib in this cohort. These values were slightly longer than those in our previous study, which reported a median PFS of 12 months using purely clinical data without survival analysis [7].

Gefitinib is generally well-tolerated but may cause certain adverse events. The most common ones are rash and diarrhoea, while less common ones include nausea, vomiting, and anorexia [23]. One specific adverse event seen in patients on TKI therapy is paronychia [24]. This retrospective analysis demonstrated that both innovator and generic gefitinib formulations were generally well tolerated in patients with *EGFR*-mutated NSCLC. However, specific AEs particularly diarrhoea, stomatitis, and paronychia occurred more frequently and with higher intensity in patients receiving the generic formulation. These findings are consistent with prior observational reports indicating that the frequency of *EGFR-TKI*–related skin and gastrointestinal toxicities may vary between formulations due to pharmacokinetic variability. Although generic products must meet bioequivalence criteria, minor differences in absorption rates or formulation components may affect local tolerability, especially in drugs with narrow therapeutic indices, such as like gefitinib. In the current study, no significant differences were observed in hepatotoxicity (as indicated by AST/ALT elevation) or neuropathy, suggesting that systemic toxicity profiles remain comparable. The higher frequency of dermatologic and mucosal events in the generic group could also reflect longer treatment duration or differential patient characteristics, though however, these variables were not

fully controlled due to the retrospective nature of the data.

These findings align with other studies identifying skin disorders as the most common adverse drug reactions [25, 26]. This occurs because gefitinib inhibits the activity of the *EGFR*, which is not only expressed in tumor cells but also plays an important role in skin function and regeneration. Inhibition of *EGFR* in the skin can lead to inflammation, decreased vascular tone, and increased vascular permeability, all of which contribute to the development of dermatologic adverse reactions [27]. Overall, the results indicate that while the generic gefitinib formulation maintains comparable safety regarding severe adverse events, certain non-serious but bothersome toxicities occur more frequently. This may have implications for treatment adherence and quality of life, especially in long-term therapy. Future prospective pharmacovigilance or pharmacokinetic studies are warranted to confirm these findings and to clarify whether formulation differences contribute to the observed variation in toxicity frequency.

Several limitations of this study warrant consideration. First, the retrospective cohort design may introduce inherent biases, such as reliance on the completeness of medical records and the potential for certain variables not being fully controlled. Second, we observed a near-significant difference in ECOG performance status at baseline, which might have influenced treatment outcomes despite our efforts to adjust for confounders. Third, the sample size in specific subgroups, particularly for uncommon *EGFR* mutation types, was relatively limited, making it difficult to draw definitive conclusions for these specific populations. Lastly, the study population was relatively homogeneous, and the follow-up period, while sufficient for PFS, may require a longer horizon to fully assess overall survival.

These findings have significant implications for the Indonesian healthcare landscape, particularly within the JKN framework, as they evaluate the specific generic product used in national procurement. Since the data were gathered from two major national referral centers, the results provide a robust reflection of real-world clinical practice in lung cancer management in Indonesia. Furthermore, given the high prevalence of *EGFR* mutations across Asian populations, our study serves as a critical reference for other middle-income countries with similar demographic profiles and healthcare systems that are transitioning toward generic oncology medicines to optimize resources.

In conclusion, this real-world study demonstrates that the generic gefitinib formulation achieves comparable clinical effectiveness to the innovator drug in terms of progression-free survival among patients with *EGFR*-mutated NSCLC. While both formulations are generally well-tolerated, the generic formulation is associated with a significantly higher incidence of certain mild-to-moderate adverse events, specifically diarrhoea, stomatitis, and paronychia.

These findings support the therapeutic equivalence of generic gefitinib for NSCLC management within clinical practice, although clinicians should implement vigilant monitoring and proactive management of dermatologic and gastrointestinal toxicities to maintain patient treatment adherence. Furthermore, given the nationwide transition to generic formulations within Indonesia's National Health Insurance (JKN) system, these results underscore the critical importance of rigorous, evidence-based evaluation of clinical efficacy and safety for all newly introduced generic oncology medicines to ensure optimal patient outcomes and preserve public trust in the healthcare setting.

Author Contribution Statement

All authors contributed essential to the concept, data, analysis, and interpretation of data; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be authors per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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Approval

This research is part of the doctoral dissertation work of Fitri Nurhayati, conducted under the Doctoral Program in Pharmacy, Faculty of Pharmacy, Universitas Pancasila, and approved by the institution's academic scientific body.

Ethical Declaration

This study was reviewed and approved by the Ethics Committees of Persahabatan National Respiratory Referral Hospital (No. 62/KEPK-RSUPP/07/2022) and Dharmais Cancer Center Hospital (No. 201/KEPK/VIII/2022). All procedures were conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments.

Conflict of Interest

The authors declare no conflict of interest related to this study.

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