ORIGINAL ARTICLE

Indirect costs and related factors for patients with non-small cell lung cancer treated with targeted therapy in Vietnam

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ABSTRACT

Indirect costs can be a burden for non-small cell lung cancer (NSCLC) patients, often overlooked due to limited data availability and challenges in measurement. This study aimed to estimate the economic burden of indirect costs and identify factors that affect them, particularly among patients of working age (under 60 years old). A cross-sectional descriptive study was conducted by interviewing 310 NSCLC patients receiving first-line targeted therapy at the Vietnam National Cancer Hospital over a 15-month period from October 2022 to December 2023. The human capital method was used to estimate indirect costs, which included expenses related to days absent from work for patients and caregivers, as well as patients' loss of income. A multivariate linear regression model was used to determine the association between patient characteristics and total indirect costs. Out of 310 NSCLC patients, 43.5% were under 60 years old. The rate of caregivers' absence from work was 49%, and 37.7% of patients experienced income loss. The monthly mean total indirect costs were $96.0, with the cost for patients' loss of income being the largest at $83.3, accounting for 86.8% of the total indirect costs. Factors such as age (under 60), gender (male), and occupation (employed or unemployed) were identified as related to an increase in the total indirect costs for NSCLC patients compared to other groups ($p < 0.05$ for each group). These findings indicate that indirect costs are a burden for NSCLC patients under 60 years old and their families.

Keywords:
non-small cell lung cancer; targeted therapy; cost, indirect cost

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INTRODUCTION

In 2022, lung cancer (LC) accounted for the highest proportion of new cancer cases worldwide, with 2.48 million new cases (12.4%) and 1.82 million deaths (18.7%).[1] By 2025, Southeast Asia is projected to have the highest number of new cases and deaths compared to other regions worldwide.[2] NSCLC makes up approximately 85% of all new cases of LC detected each year.[3]

The average annual cost of treating LC is reported to be $45,000 in the United States,[4] and $43,336 in China.[5] Direct costs, which can be easily collected and measured in practice,[6] can be obtained from health care system databases[7–9] or administrative databases.[10] In contrast, indirect costs resulting from a decrease in labor productivity include reduced productivity at home and at work, as well as missed workdays.[11] These costs are often not readily available and are challenging to identify, measure, or calculate.[6] Therefore, indirect costs are rarely mentioned in health economic studies, even though they are particularly significant,[12] and sometimes even larger than direct costs.[11] Excluding indirect costs from the total may underestimate the actual cost of treating the disease.[13] Additionally, age groups and the duration of the disease since diagnosis are the main factors related to the indirect costs of NSCLC patients in China.[14]

In Vietnam, over 80% of LC cases are diagnosed as NSCLC.[15] In a developing country like Vietnam, social welfare remains low. Health insurance agencies do not cover the indirect costs associated with patients' income loss and absence from work, which can become a significant economic burden for NSCLC patients. Additionally, no studies have been conducted to estimate the indirect costs for these patients in Vietnam. Therefore, this study was conducted to estimate the economic burden of indirect costs, evaluate the factors influencing them, and investigate whether working-age patients (under 60 years old) are the main subjects bearing the economic burden of indirect costs. The study also aims to propose some appropriate policies to reduce the burden on NSCLC patients and their families.

METHODS

Study population

The study subjects were all NSCLC patients with characteristics such as EGFR (Epidermal Growth Factor Receptor) gene mutation, diagnosed at stage IV, and receiving first-line outpatient treatment with targeted therapy. The criteria for selecting patients included the ability to answer the interview in Vietnamese, absence of neurological problems or psychiatric disorders, and written agreement to participate in the study before the interview. Cases excluded from this study were patients who had received second-line or third-line treatment, were being diagnosed or suspected of disease progression, or had other acute diseases.

NSCLC patients can appoint their caregivers to serve as their representatives for signing the consent form to participate in the study and be interviewed directly. Caregivers must meet specific criteria: they must be family members of the patient (such as a spouse, children, parents, or siblings), be at least 18 years old, provide regular care for the patient, have a comprehensive understanding of the patient's issues, be able to actively listen, comprehend, and respond to questions about the study in Vietnamese, and not have any cognitive disorders.

Study design

To estimate the indirect costs of patients with NSCLC, we conducted a cross-sectional descriptive study using

face-to-face interviews from October 2022 to December 2023. The interviews took place at two lung cancer intensive treatment departments (Medical Oncology 1 and Medical Oncology 2) of the Vietnam National Cancer Hospital in Tan Trieu.

Sample size: In order to estimate the sample size needed for this study, we applied the formula for calculating the mean value: $\mathbf{n = (Z^2_{1-\alpha/2}\ \sigma^2)/\ \varepsilon^2\ \mu^2}$

The values in the formula above include: n, the sample size required for the study; $Z_{1-\alpha/2}$ = 1.96 (when α = 0.05); **ε**, expected error (ε = 0.136); μ, the average indirect cost of the reference study, which was MYR 2864.49 ($682.02);[11] and σ, the standard deviation of indirect cost in the reference study, which was MYR 3319.31 ($790.31).[11] Results showed that n = 278.9 patients. To account for cases where study questionnaires were collected with missing information, we added 10% to the sample size, resulting in the desired sample size of 306.8 (307) patients. In actuality, our study collected 310 questionnaires from NSCLC patients with information to serve the study.

Research sampling method: In this study, we used a convenience sampling method by inviting all eligible patients attending their monthly hospital visits to participate.

The questions and measurements: Pre-prepared questionnaires were used to gather general patient characteristics and the average indirect costs per month for NSCLC patients from the time of their diagnosis until the interview.

Data collection method: Patients who had completed clinical and paraclinical examinations, and were either waiting for targeted drugs to be dispensed for home treatment or had already received the drugs and were preparing to go home, were invited by the researcher to participate in this study. Patients and their caregivers were provided with explanations about the study and given a form outlining its purpose, steps, questions for patients and caregivers, and tasks to be completed. The researcher answered all of their questions until they had no more related questions. Face-to-face interviews were conducted with 310 NSCLC patients who met the criteria and agreed to participate in writing. These interviews took place in a private room to ensure privacy and allow patients or caregivers to answer questions about costs honestly and comfortably, without being influenced by other patients around them.

How to calculate Indirect costs

Indirect costs refer to the loss of productivity experienced by patients and their families, resulting in a decrease in both short-term and long-term working capacity due to the treatment process.[11] These costs encompass all productivity losses incurred by NSCLC patients and their caregivers from the moment of NSCLC diagnosis to the time of the interview.[14,16] In this study, the human capital method was used to calculate the productivity losses of both patients and caregivers.

In Vietnam, there is no detailed system to track the number of days of absence and individual salaries. Consequently, the number of absence days and salaries of patients and caregivers were determined based on information provided during interviews. Additionally, patients and their caregivers were requested to report their average monthly income before and after their illness up to the time of the interview.[14] Patients and their caregivers were asked to recall the number of days they had been absent from work, including business or home, in the one recent month before the interview. According to the Law on Social Insurance (2014) and the Labor Code (2019) of Vietnam, the standard working day used to calculate monthly wages for employees is 8 hours per day and 24 days per month. The average daily income of patients and their caregivers will be calculated by dividing the average

monthly income self-declared by the patient by 24 standard working days. For the unemployed or homemakers of working age, income has been calculated based on the minimum wage according to the four regions of Vietnam for one person per month and one working hour according to Decree No. 38/2022/ND-CP of the Government (2022). Patients who are beyond working age or have retired (60 years and 9 months for men, 56 years for women) but are still able to do housework, laundry, childcare, and cooking means that the effective working hours to calculate income are 6 hours per day or 18 days per month compared to normal healthy people, multiplied by the minimum wage per month according to the four regions of Vietnam (2022).[11,17] Therefore, indirect costs include:

(1) Patients' absence cost (**PAC**), and (2) caregivers' absence cost (**CAC**) from work were calculated by multiplying the average daily income by the number of days taken off in a month. Vacation days were not included in the calculation of costs. (3) Patients' income loss cost (**PILC**) was calculated by subtracting the patient's average monthly income before and after the illness.

The total indirect costs for a patient in a month were calculated using the following formula:

Total indirect costs = PAC + CAC + PILC

Data analysis and processing

All data on indirect costs and characteristics of 310 patients were collected and coded using Excel 2019 software. The data were then transferred to SPSS 26.0 and STATA 17.0 software for analysis. The component costs of indirect costs and total indirect costs have been standardized in Vietnamese Dong according to the 2023 consumer price index (CPI) published by the General Statistics Office of Vietnam.[18] All indirect costs have been converted to US dollars in 2023 based on the exchange rate announced by the Ministry of Finance of Vietnam (No. 6885/TB-KBNN; announcement date: November 30, 2023). During that period, one US dollar was equivalent to 23,993 VND.

We tested the cost variables for normal distribution using the Kolmogorov-Smirnov test and histogram charts. The results indicated that the indirect costs were not normally distributed. Therefore, we utilized the Mann-Whitney U and Kruskal-Wallis H tests to assess differences in independent variables with two or more groups. Pearson correlation analysis was conducted between independent variables to check for multicollinearity. Any results below 0.7 were retained and entered into the multivariate linear regression model.[19,20] To analyze the factors associated with total indirect costs, we used a multivariate linear regression model assuming that total indirect costs follow a normal distribution.

Ethical approval

Our study was approved under certificate numbers 666/GCN-HDDDNCYSH-DHYHN, dated August 30, 2022, and 974/GCN-HDDDNCYSH-DHYHN, dated August 6, 2023, by the Ethics Council of Hanoi Medical University. We also obtained permission from the leadership of Vietnam National Cancer Hospital to collect and utilize data for research purposes.

RESULTS

General characteristics of the research subjects

According to the study results in **Table 1**, out of the 310 patients with NSCLC, 43.5% (135/310) were under 60 years old, and 51.0% were female. The

highest education level completed by patients was secondary school (49%), while the lowest was primary school (6.5%). The patients were mainly farmers and workers (44.2%), with over half of them (65.2%) having an illness duration of 12 months or less. The average monthly income of patients was $117.2. The rate of patients responding to treatment was quite stable at 93.2%, but 66.5% experienced at least one side effect. There were statistically significant differences between the occupations, income, and age groups of patients ($p < 0.05$ for each group).

Indirect costs of non-small cell lung cancer patients

The components of indirect costs for NSCLC patients included costs for patients' absence from work, caregivers' absence from work, and patients' income loss. The rate of caregivers' absence from work was the highest at 49%, followed by patients experiencing income loss at 37.7%, and patients' absence from work had the lowest rate at 18.1% (**Figure 1**).

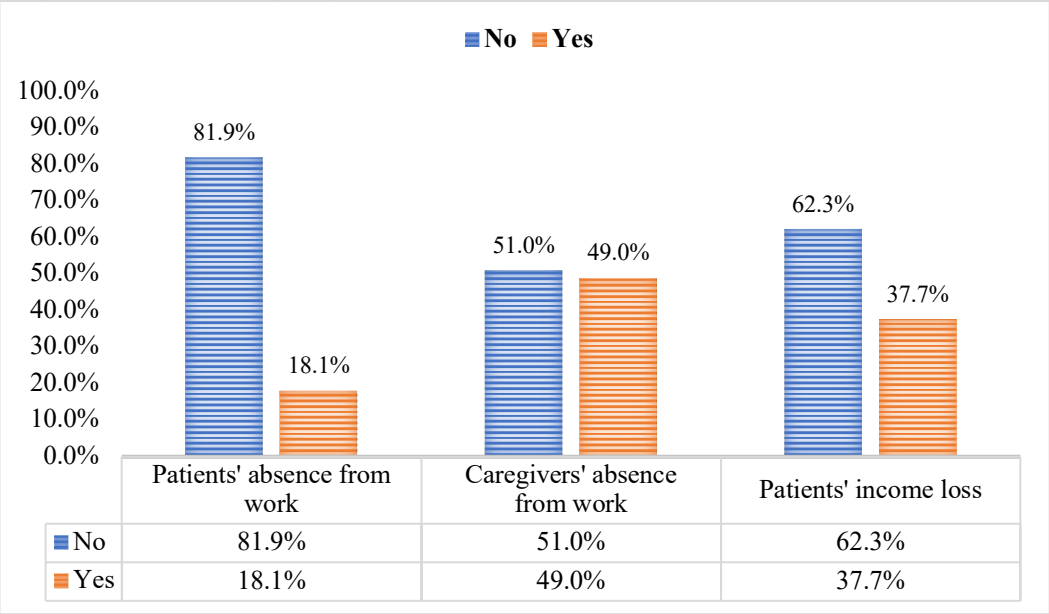


Figure 1. The proportion of patients and caregivers experiencing losses from indirect costs

Table 1. General characteristics and age groups of the study population (n = 310)

Characteristics	Total n (%)	Age groups (years) n (%)				p value
		< 50 (n = 44)	50-59 (n = 91)	60-69 (n = 122)	≥ 70 (n = 53)	
Gender						
Female	158 (51.0%)	21 (6.8%)	54 (17.4%)	56 (18.1%)	27 (8.7%)	0.262
Male	152 (49.0%)	23 (7.4%)	37 (11.9%)	66 (21.3%)	26 (8.4%)	
Education level						
Intermediate or higher	36 (11.6%)	10 (3.2%)	8 (2.6%)	11 (3.5%)	7 (2.3%)	
High school	102 (32.9%)	13 (4.2%)	31 (10.0%)	38 (12.3%)	20 (6.5%)	
Secondary school	152 (49.0%)	21 (6.8%)	45 (14.5%)	61 (19.7%)	25 (8.1%)	0.129
Primary school or lower	20 (6.5%)	0 (0.0%)	7 (2.3%)	12 (3.9%)	1 (0.3%)	

Characteristics	Total n (%)	Age groups (years) n (%)				p value
		< 50 (n = 44)	50-59 (n = 91)	60-69 (n = 122)	≥ 70 (n = 53)	
Occupation						
Retired	89 (28.7%)	0 (0.0%)	7 (2.3%)	48 (15.5%)	34 (11.0%)	**<0.001 *** **
Farmer or Worker	137 (44.2%)	12 (3.9%)	55 (17.7%)	55 (17.7%)	15 (4.8%)	
Freelancers	34 (11.0%)	8 (2.6%)	15 (4.8%)	9 (2.9%)	2 (0.6%)	
Employment or business	32 (10.3%)	14 (4.5%)	8 (2.6%)	8 (2.6%)	2 (0.6%)	
Unemployed since illness	18 (5.8%)	10 (3.2%)	6 (1.9%)	2 (0.6%)	0 (0.0%)	
Patients income (USD/month)						
Mean (SD)[b]	117.2 (211.9)	214.1 (410.9)	94.1 (178.6)	92.7 (134.8)	132.5 (138.2)	**0.019***
Duration of illness (months)						
> 24	38 (12.3%)	3 (1.0%)	13 (4.2%)	15 (4.8%)	7 (2.3%)	0.474
13-24	70 (22.6%)	11 (3.5%)	17 (5.5%)	25 (8.1%)	17 (5.5%)	
≤ 12	202 (65.2%)	30 (9.7%)	61 (19.7%)	82 (26.5%)	29 (9.4%)	
Response evaluation						
Partial response	21 (6.8%)	3 (1.0%)	9 (2.9%)	8 (2.6%)	1 (0.3%)	0.332
Stable disease	289 (93.2%)	41 (13.2%)	82 (26.5%)	114 (36.8%)	52 (16.8%)	
Side effects						
Yes	206 (66.5%)	26 (8.4%)	63 (20.3%)	84 (27.1%)	33 (10.6%)	0.548
No	104 (33.5%)	18 (5.8%)	28 (9.0%)	38 (12.3%)	20 (6.5%)	

*p-value: Pearson chi-square test or Fisher test, [b]Kruskal–Wallis H test, *p<0.05, **p<0.01, ***p < 0.001.*

The average total indirect costs per month for NSCLC patients were $96.0. Among these monthly indirect costs, the highest cost was PILC at $83.3, accounting for 86.8%. This was followed by CAC at $10.1, which accounted for 10.6%. PAC was the lowest at $2.5, making up only 2.6% of the total indirect costs (**Table 2**).

Table 2. Total indirect costs for NSCLC patients (n = 310, 2023 USD)

Indirect costs *(USD/month)*	Mean	Standard deviation	Median	Minimum	Maximum	% of total indirect cost
PAC	2.5	9.8	0.0	0.0	90.4	2.6%
CAC	10.1	15.0	0.0	0.0	125.0	10.6%
PILC	83.3	138.5	0.0	0.0	625.2	86.8%
Total indirect costs	96.0	138.8	20.8	0.0	650.2	100.0%

The results in **Table 3** show that PAC per month was highest in patients under 50 years old ($10.9) and decreased gradually to $0.0 for those aged 70 years and older ($p < 0.001$). Similarly, PILC per month was highest in patients under 50 years old ($218.9) and decreased gradually to only $0.8 for those aged 70 years and older ($p < 0.001$). However, the differences between CAC and patients' age groups were not statistically significant ($p > 0.05$).

Table 3. Cost components of indirect costs and age groups of NSCLC patients (n = 310, 2023 USD)

Age groups (years)		Components of total indirect costs *(USD/month)*		
		PAC	**CAC**	**PILC**
< 50	Mean	10.9	6.9	218.9
	SD	22.2	11.9	190.7
50-59	Mean	2.6	9.6	108.6
	SD	6.7	16.9	129.6
60-69	Mean	0.6	10.5	51.4
	SD	2.2	14.8	111.4
≥ 70	Mean	0.0	12.9	0.8
	SD	0.0	13.9	5.7
p value		**<0.001[b], *****	0.080[b]	**<0.001[b], *****

*SD: Standard deviation, [a]Mann–Whitney U test, [b]Kruskal–Wallis H test, ***p < 0.001.*

Factors affecting the total indirect costs of NSCLC patients

According to the results of the multivariate linear regression model in **Table 4**, factors such as age (under 60 years) and occupation (employed or unemployed) were associated with increased indirect costs in NSCLC patients compared to the group aged 70 years and older and the retired group ($p < 0.05$ for each group). Additionally, male patients showed a correlation with higher indirect costs compared to females (Beta = 1328003, $p < 0.001$).

Table 4. Factors affecting the total indirect costs of NSCLC patients (n = 310)

Independent variables	Total indirect costs (Linear regression model)					
	Univariate			Multivariate		
	Beta	**S.E**	**p value**	**Beta**	**S.E**	**p value**
Intercept	-	-	-	-487836.2	1403265	0.728
Age groups (years)						
≥ 70	Reference	-	-	Reference	-	-
60-69	**1171108**	480285.2	**0.015***	735803.1	429806.2	0.088
50-59	**2572768**	504452.9	**<0.001*****	**1559777**	495737.2	**0.002****
< 50	**5349920**	595414.8	**<0.001*****	**2664379**	618073.1	**<0.001*****
Gender						
Female	Reference	-	-	Reference	-	-
Male	**1300511**	371678.6	**0.001****	**1328003**	296281.4	**<0.001*****
Education level						
Primary school or lower	Reference	-	-	Reference	-	-
Secondary school	1364556	790662.4	0.085	1089044	616430.8	0.078
High school	1083328	812883.9	0.184	658183.5	660621.9	0.320
Intermediate or higher	1784892	927025	0.055	1414419	793408.2	0.076
Occupation						
Retired	Reference	-	-	Reference	-	-
Farmer or Worker	**1373903**	365033.6	**<0.001*****	**906830.9**	444734.5	**0.042***
Freelancers	**3357140**	540570.1	**<0.001*****	**2365830**	579861.3	**<0.001*****
Employment or business	**3797653**	552658.3	**<0.001*****	**2514877**	591683.7	**<0.001*****
Unemployed since illness	**8088105**	692938.4	**<0.001*****	**6446530**	758110.1	**<0.001*****

Independent variables	Total indirect costs (Linear regression model)					
	Univariate			Multivariate		
	Beta	S.E	p value	Beta	S.E	p value
Duration of illness (months)	-11182.5	13737.48	0.416	-3827.121	10754.55	0.722
Response Evaluation						
Partial response	Reference	-	-	Reference	-	-
Stable disease	-1047261	751552.3	0.164	-520522	582292	0.372
Side effects						
No	Reference	-	-	Reference	-	-
Yes	-262973	400986	0.512	-209200.7	310327.9	0.501
				Prob > F	=	0.0000
				R-squared	=	0.4513
				Adj R-squared	=	0.4253

Reference: Beta = *1, S.E: Standard error, *p < 0.05, **p < 0.01, ***p < 0.001.*
Note: In the linear regression model, we have relied on the assumption that total indirect costs are normally distributed.

DISCUSSION

The average indirect cost per month of outpatient treatment with targeted therapy for NSCLC patients was $96.0. Meanwhile, the rate of patients' absence from work was 37.7%, but only 5.8% of patients experienced unemployment as a result of their illness. However, within the total average indirect costs per month, the cost for patients' income loss accounted for the highest proportion (86.8%). Research results in China showed that when NSCLC patients were diagnosed at stage IV, they primarily chose to stay at home to treat the disease. This issue can be attributed to the prolonged treatment process, which can increase the likelihood of patients becoming unemployed in both the short and long term.[14] This may explain why the cost of patients' income loss accounts for the highest proportion of total indirect costs. Remarkably, in the context of Vietnam, health insurance agencies do not cover the indirect costs associated with patients' income loss and absence from work. Therefore, these costs can become a significant economic burden for NSCLC patients.

Additionally, the average indirect cost per month for NSCLC patients accounted for 81.9% of the average monthly income remaining for the patients ($96.0 compared to $117.2). These costs were a significant economic pressure for NSCLC patients. On the other hand, the rate of caregivers' absence from work was 49%, with the cost of caregivers' absence making up 10.6% of the total monthly indirect costs for NSCLC patients. This means that the treatment of NSCLC not only reduces labor productivity for patients but also for caregivers. It is important to note that all indirect costs resulting from the absence and/or income loss of patients and their caregivers were not covered or compensated by any insurance agencies. Consequently, patients and their families may encounter challenges related to financial risks and burdens.[7,13,21] Patients facing financial burdens may seek to reduce treatment costs in various ways, such as dose reduction, treatment discontinuation, and noncompliance with prescribed treatment regimens.[21–25] The consequences may lead to a reduced quality of life, increased symptoms, decreased survival, and shortened survival time.[21,26,27] Therefore, the next objective of this study will be to identify factors that increase indirect costs based on the characteristics of NSCLC patients.

Our study found associations

between patients' absences, income loss costs, and their age groups. The costs were significantly higher in age groups under 60 ($p < 0.001$ for each group). Similarly, in a linear regression model, the total indirect costs were related to age groups (under 60, $p < 0.001$). This finding is consistent with a study conducted in China.[14] Patients under 60 years old constitute the primary workforce in society. When illness strikes at a younger age, there is a higher increase in indirect costs, which may surpass direct costs.[11] Therefore, research focused on estimating indirect costs is just as crucial as estimating direct costs for NSCLC patients.

Indirect costs were found to be associated with the gender of NSCLC patients, with male patients incurring higher indirect costs than female patients (Beta = 1328003, $p < 0.001$). This finding is consistent with a study conducted in Greece.[16] Additionally, the total indirect costs for NSCLC patients were related to their occupation ($p < 0.05$ for each group). However, a study in China did not find any association between gender and indirect costs, with only occupation showing a relation to the indirect costs of NSCLC patients.[14] The discrepancies in research results can be attributed to various factors, including the use of different treatment models, characteristics of the research subjects, choice of unit costs, differences in the health care systems of each country, research design, and the methods used to estimate costs in each study.[16,28]

In Vietnam, the Social Insurance Agency does not cover indirect costs such as absenteeism from work and reduced productivity for NSCLC patients. Therefore, solutions to reduce the burden of indirect costs for NSCLC patients need to be considered. Firstly, patients should take the initiative to seek out new job opportunities or adjust their current job positions to better suit their health status. Secondly, the government should implement policies that encourage and support businesses to hire NSCLC patients, particularly those under 60 years of age who are currently unemployed. Lastly, the government should establish policies to support NSCLC patients, including vocational training, career counseling, and assistance in finding new jobs that align with the patients' health needs.

Strengths and limitations

Our study is one of the first to estimate the indirect costs of NSCLC patients with stage IV EGFR mutations receiving first-line targeted therapy in Vietnam. However, our study also had some limitations. Firstly, the research was conducted at only one hospital in Vietnam and was a cross-sectional study conducted over a one-month period. This may not provide a comprehensive representation of all indirect costs incurred by patients throughout their entire treatment process in the country. Secondly, the use of convenience sampling may have introduced potential bias into this study. Thirdly, the study mainly focuses on patients receiving first-line targeted therapy so there will be a lack of control or comparison groups, such as patients receiving second-line or third-line targeted therapy, those not receiving targeted therapy or those with different types of health insurance. This limitation could restrict the generalizability and contextual interpretation of the findings. Finally, there is a potential for recall errors when reporting the number of days absent from work and income per month for patients and caregivers, which could impact the accuracy of the estimates for indirect costs.

RECOMMENDATIONS

These indirect costs not only negatively impact patients and household finances but also affect the treatment outcomes of NSCLC patients. A comprehensive approach involving the government, NSCLC patients, and businesses would assist NSCLC patients in

retaining their current jobs or securing new, suitable employment opportunities. This would help alleviate the economic strain caused by indirect costs for NSCLC patients and their families.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology: Chinh Van Nguyen, Huong Thi Thanh Tran, Kiet Tuan Pham Huy. Data curation and investigation: Chinh Van Nguyen. Formal analysis and software: Chinh Van Nguyen, Kiet Tuan Pham Huy. Supervision: Kiet Tuan Pham Huy, Huong Thi Thanh Tran. Validation and Visualization: Chinh Van Nguyen, Kiet Tuan Pham Huy, Huong Thi Thanh Tran. Writing – original draft: Chinh Van Nguyen. Writing – review & editing: Chinh Van Nguyen, Huong Thi Thanh Tran, Kiet Tuan Pham Huy.

ETHICAL CONSIDERATION

The study protocol was approved by the Board of Directors of the Vietnam National Cancer Hospital (Reference number: 12a/TTr-VUT, dated October 07, 2022). Ethical clearance was also obtained from the Hanoi Medical University Institutional Ethical Review Board (HMU IRB) with reference numbers: 666/GCN-HĐĐĐNCYSH-ĐHYHN (August 30, 2022), and 974/GCN-HĐĐĐNCYH-ĐHYHN (August 06, 2023). All participants provided written informed consent prior to their inclusion in the study.

Trial Registration: Not applicable. This is an observational study and does not require registration on the WHO ICTRP platform.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest regarding this study.

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