The Relationship Between Clinical Risk Factors and Patient's Survival Rate in Non-Small Cell Lung Carcinoma Cases: A Cross-Sectional Study

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ABSTRACT

Background: Non-small cell carcinoma (NSCLC) is the most common type of lung cancer. Risk factors for lung cancer include smoking, genetic factors, chronic lung disease, lung infections, radon exposure, air pollution, exposure to carcinogenic substances in the workplace and other risk factors. The significance of each of these risk factors differs by sex, race and region in a given country.
Purpose: The study was conducted to assess the analysis of risk factors, treatment response and survival of NSCLC patients.
Methods: Cross sectional and survival analysis, patients undergoing diagnostic and treatment at Dr. Wahidin Sudirohusodo Makassar period January 2017-December 2019. Anamnesis of risk factors and survival by telephone and patient medical record data.
Results: There are 100 patients who fulfill the inclusion criteria; Subject characteristics were mostly male (64%), age >45 years (84%), Bugis ethnicity (50%), farmer occupation (27%), active smokers (60%), consume filter cigarettes (75%), and has severe brinkman index (BI) (51.6%). About 40% of the subjects were non-smokers, 50% of whom were passive smokers. Severe IB and high-risk occupations by type of KPKBSK were significant (p = 0.02 and p = 0.01). Age <45 years, median survival was better than age 45 years (8 months versus 4 months), p = 0.002. Subjects receiving EGFR-TKI had a better median survival of 7 months, platinum doublet 6 months, did not receive treatment for 2 months, p = <0.05.
Conclusion: Brinkman Index (BI) and high-risk occupation based on NSCLC type are significant. Age < 45 years had a good median survival. Subjects who received TKI had a better median survival.

Keywords: Non-small cell lung carcinoma, clinical risk factors, survival rate.

INTRODUCTION

Lung cancer is the biggest cause of cancer-related mortality worldwide, and its prevalence has risen over the past three decades. The number of new instances of lung cancer in males is projected to be the greatest in 2020, with 1,4 million new cases (14.3 % of all malignancies in men), and the third highest in women, with 770,000 new cases (8.4 % of all cases). cancer.(1)

Non-small cell lung carcinoma (NSCLC) comprises approximately 85 % of all lung malignancies. According to the study's findings, just 15% of lung cancer cases were discovered at an early stage. Approximately two-thirds of lung cancer patients are in a metastatic state at the time of diagnosis. Smoking, hereditary factors, chronic lung illness, lung infections, radon exposure, air pollution, occupational exposure to carcinogenic compounds, and other risk factors are associated with NSCLC. (2)

Several studies have found that a family history of lung cancer is also connected with the risk of NSCLC. Certain families have a hereditary and genetic predisposition to cancer, and genomic instability in some individuals causes lung cancer.(3) Chronic inflammation, such as Chronic Obstructive Pulmonary Disease (COPD), raises the risk of NSCLC in developing countries. In addition, lung infections such as pulmonary tuberculosis infection enhance the incidence of non-small cell lung cancer.(4) In addition, exposure to natural radiation such as radon raises the risk of non-small cell lung cancer.(5)

The patient's performance status upon diagnosis, cancer stage, histological type, tumor molecular markers such as Epidermal Growth Factor Receptor (EGFR) mutations, comorbidities, nutritional state, and treatment, according to the literature. However, risk variables including as smoking history, gender, and age can also influence NSCLC survival.(6,7)

Despite the fact that cigarette smoke exposure, genetic susceptibility, air pollution, radon exposure, lung infection, chronic lung disease, and certain occupational exposures have been identified as major risk factors that can affect NSCLC survival, the significance of each of these risk factors varies by gender, race, and region within a country. Therefore, it is vital to investigate the association between risk variables, treatment response, and the survival of advanced NSCLC patients.

METHOD

Research design
This research is a study with a cross sectional design and survival analysis. The research was conducted at the Department of Pulmonology and Respiratory Medicine, RSUP Dr. Wahidin Sudirohusodo Makassar, data collection for the period January 2017-December 2019. Data collection period 1 January – 1 March 2022.

Subject
The participants in this study were all lung cancer patients with non-small cell carcinoma whose diagnosis was confirmed through cytological and or histopathological examinations who underwent therapy at Dr. RSUP. Wahidin Sudirohusodo Makassar. The inclusion criteria for this study were all patients diagnosed with non-small cell lung cancer at Dr. RSUP. Wahidin Sudirohusodo Makassar and has been confirmed by cytology and/or histopathology, is willing to participate in the study by signing the informed consent and is willing to be interviewed by telephone.

Data collection
The identity of the patient who met the inclusion criteria was tracked from the patient's medical record data, was given a complete explanation of the information to be carried out on the subject and if agreed, the subject would fill out and sign the informed consent. Research subjects who met the inclusion criteria were interviewed via telephone (the patient concerned and/or the patient's family), the results of the interviews were recorded and recorded to explore information on risk factors and NSCLC survival.

Data analysis
Data normality test using Kolmogorov-Smirnov/Shapiro-Wilk. Numerical data analysis used unpaired T-test with alternative Mann-Whitney test. To see the correlation between risk factors and NSCLC, the Spearman correlation test was carried out. Analysis of the relationship on categorical variables was carried out with the Chi-Square test. Multivariate analysis was conducted to assess the relationship between two or more dependent variables using logistic regression test. Survival analysis using Kaplan Meier analysis. The significance level of = 5% or 0.05 and = 95%. If $p < 0.05$ then there is a relationship or difference between the two variables. If p 0.05 then the difference that occurs by chance or is not significant.

RESULTS

Sampling of the research was carried out at Dr. RSUP. Wahidin Sudirohusodo Makassar is a lung cancer patient during the period January 2017 – December 2019 who was followed up until March 1, 2022 to assess survival retrospectively. Total subjects who met the inclusion criteria were 100 subjects consisting of 49 subjects with cytology/histology of Adenocarcinoma, 37 subjects with Squamous Cell Carcinoma (SCC), 5 subjects with Adenosquamous type and 9 subjects with NSCLC that could not be determined or Not Otherwise Specified (NOS).

Patient Characteristics

The basic characteristics of NSCLC patients can be seen in table 1. Most of the research subjects were male 64 subjects (64%) and female 36 (36%). Subjects with the highest education level graduated from Elementary School (SD) 31 subjects (31%), High School (SMA) 28 subjects (28%), Bachelor (S1) 21 subjects (21%). Subjects with age 45 years were 84 subjects (84%), and age <45 years were 16 subjects (16%). The largest ethnic group is the Bugis ethnic group with 50 subjects (50%), followed by the Toraja ethnic group with 18 subjects (18%), the Makassar ethnic group with 17 subjects (17%). Most of the research subjects came from the province of South Sulawesi with 76 subjects (76%), while the provinces of West Sulawesi and Southeast

Sulawesi each had 8 subjects (8%). The distribution of subjects from the province of South Sulawesi consisted of Makassar City contributing 24 subjects (24%), Kab. Toraja 7 subjects (7%), Kab. Sidenreng Rappang (Sidrap) 6 subjects (6%) while Kab. Maros and Pinrang each 5 subjects (5%).

There were 14 subjects (14%), with the highest type of pollution being pollution from factory smoke (8%). Interestingly, houses with wooden floors (houses on stilts) are lower than houses with cement or tile floors (24% compared to 76%). Farmers are the most common type of work, 27% of the subjects, followed by housewives (IRT) as much as 17%. There are 74 subjects (74%). Active smokers were found in 60 subjects (60%), consisting of 31 subjects (51.6%) with severe IB, moderate IB in 19 subjects (31.6%) and light IB in 10 subjects (16.6%). Meanwhile, out of 40 subjects (40%) were non-smokers, there were 20 subjects (50%) who were passive smokers. Subjects of active smokers used filtered cigarettes in 45 subjects (75%), and unfiltered cigarettes in 15 subjects (25%). There was a family history of cancer in 26 subjects (26%), consisting of a family history of lung cancer in 5 subjects (19.3%) and a family history of other cancers in 21 subjects (80.7%). There was a history of chronic lung disease in 3 subjects (3%) in the form of a history of being diagnosed with Pulmonary Tuberculosis.

Table 1 Characteristics of research subjects

SUBJECT CHARACTERISTIC	N (N = 102)	%AGE (%)
Gender		
Man	64	64
Woman	36	36
Age		
< 45 years old	16	16
45 years	84	84
Level of education		
Not completed in primary school	6	6
Elementary school	31	31
Junior High School	10	10
Senior High School	28	28
Diploma	4	34
Barchelor	21	21
Ethnic group		
Bugis	50	50
Toraja	18	18
Makassar	17	17
Other ethics*	15	15

Table 1 To Be Continued…		
Air pollution at home		
Factory	8	8
Motor vehicle smoke	6	6
Work		
Farmer	27	27
IRT	17	17
Teacher	9	9
Other jobs***	47	47
Exposure risk in the work environment		
High risk job	74	74
Low risk job	26	26
Active smoker	60	60
Do not smoke	40	40
Passive smoker	20	50
IB		
heavy IB	31	51,6
Medium IB	19	31.6
light IB	10	16.4
Cigarette type		
Filter	45	75
Non-Filter	15	25
Family history of cancer	26	26
Family history of lung cancer	5	19.3
Family history of other malignancies	21	80.7
History of chronic lung disease		
Pulmonary tuberculosis	3	3

Information :

Other ethnic groups*: Ambonese, Buol, Buton, Javanese, Mandar and Chinese

Other provinces/districts/cities ** : Maluku, Central Sulawesi, Gorontalo, West Papua provinces.

Other occupations*** : Unemployed, Labor, Trader, Firefighter, Employee, Construction Worker, Workshop Mechanic, Field Supervisor, Entrepreneur, Village Officer, Government Employee, Traffic Police, Security, Army Personnel, Furniture Builder, Entrepreneur.

Characteristics of NSCLC lesions

The most common type of cytology/ histology was Adenocarcinoma 49 samples (49%), followed by Squamous Cell Carcinoma (SCC) 37 subjects (37%), NSCLC NOS 9 subjects (9%) and Adenosquamous Cell Carcinoma (SCC) 5 subjects (5%). The majority of subjects at the time of diagnosis were in stage IVa (70.6%). After establishing the diagnosis, 45 subjects (45%) received platinum doublet-based chemotherapy, 23 subjects (23%) with EGFR mutations received TKI, and 33 subjects (33%) did not receive therapy for several reasons, such as; the patient refused treatment, the patient died after the diagnosis was established, and the patient's condition did not allow chemotherapy. The majority of the subjects had died when this study was completed, totalling 96 subjects (96%). This can be seen in table 2.

Table 2. Histology characteristic NSCLC		
SUBJECT CHARACTERISTIC	**N (N = 102)**	**%AGE (%)**
Cytology/Histology		
Adenocarcinoma	49	49
KSS	37	37
NSCLC NOS	9	9
Adenosquamous	5	5
Stadium		
IIIb	14	14
IIIc	2	2
IVa	72	72
IVb	12	12
Type of Treatment		
Patinum Doublet	45	45
Tyrosine Kinase Inhibitors (TKIs)	22	22
No chemotherapy/TKIs	33	33

Relationship between NSCLC Risk Factors and NSCLC Cytology/Histology Type

The type of cytology/histology of NSCLC in the age group is presented in table 4.2.1 below, divided into age groups <45 years and 45 years. In this study, the risk factor for age was not statistically significant with the type of cytology/histology of NSCLC (p > 0.05). Similarly, gender was not significantly different between men and women. There was no significant difference in the type of NSCLC cytology/histology based on ethnicity in this study (p=0.13), as well as the address of the subject by province (p=0.98).

Tabel 3. NSCLC Risk Factors compare to NSCLC Cytology/Histology Type

Characteristic	Adenocarsinoma	KSS	NOS	Adenoscuamosa	p-value
Age					0.160
Age < 45 years old	5	8	3	0	
Age 45 years old	44	29	6	5	
Gender					0.340
Man	32	21	8	3	
Woman	17	16	1	2	
Ethnic group					0.130
Ambon	0	1	0	0	
Bugis	23	18	7	2	
Buol	1	0	0	0	
Buton	0	1	0	0	
Java	4	0	0	0	
Makassar	7	7	0	3	
Mandarin	2	2	0	0	
Chinese	0	2	2	0	
Toraja	12	6	0	0	
Cigarette type					0.350
Filter	19	17	6	3	
Non-filter	10	4	1	0	
Brinkman index Category					0.020
Low	3	4	2	1	
Medium	4	10	4	1	
High	22	7	1	1	
Passive smoker	10	8	1	1	
Not a passive smoker	39	29	8	4	
Exposure risk in the work environment					0.010
Low risk job	19	7	0	0	
High risk job	30	30	9	5	
Family history of cancer					0.200
Yes	10	10	3	3	
No	39	27	6	2	

Survival Rate Analysis (Kaplan-Meier)

Survival analysis based on time from diagnosis of NSCLC until the patient's death or the end of the study, obtained survival results for NSCLC patients using the Kaplan-Meier method of survival analysis. Survival rates for NSCLC based on risk factors were assessed as Median Survival and Overall Survival. A total of 102 subjects met the criteria for this study, followed by progress until March 1, 2022, at the end of the study, 4 subjects lived (4%) and 96 subjects died (96%). A detailed description of the patient's survival risk factors is shown in table 4 and figure 1-7.

Tabel 4. Relationship between NSCLC risk factors and patients' survival rate

Risk Factors	*Median survival* dalam bulan (95% *Confidence Interval*)				Nilai p
	Estimate	*Std. Error*	*Min*	*Max*	
Age					0.002
< 45 years old	8	4.6	0.0	17.1	
>=45 years old	4	0.5	2.8	5.1	
Gender					0.900
Man	4	0.61	2.79	5.2	
Woman	5	1.19	2.65	7.34	
Ethnic group					0.330

Table 4 To Be Continued…					
Ambon	1	-	-	-	
Bugis	4	0.78	2.4	5.5	
Buol	14	-	-	-	
Buton	12	-	-	-	
Java	1	-	-	-	
Makassar	5	1.17	2.69	7.3	
Mandarin	3	12.5	0.0	27.5	
Chinese	4	2	0.08	7.92	
Toraja	3	1.27	0.5	5.49	
Type of house floor					0.410
Wood (Stilt House)	4	1.2	1.6	6.3	
Tile/cement	5	0.6	3.7	6.2	
Cigarette type					0.460
Filter	5	0.6	3.8	6.1	
Non-filter	3	0.9	1.1	4.8	
Brinkman index Category					0.120
Low	6	1.58	2.9	9	
Medium	4	1.63	0.8	7.19	
High	4	0.92	2.22	5.77	
Passive smoker	7	1.1	4.8	9.1	
Not a passive smoker	4	0.4	3	4.9	
Exposure risk in the work environment					0.500
Low risk job	5	1.00	2.8	7.1	
High risk job	3	0.72	1.5	4.4	
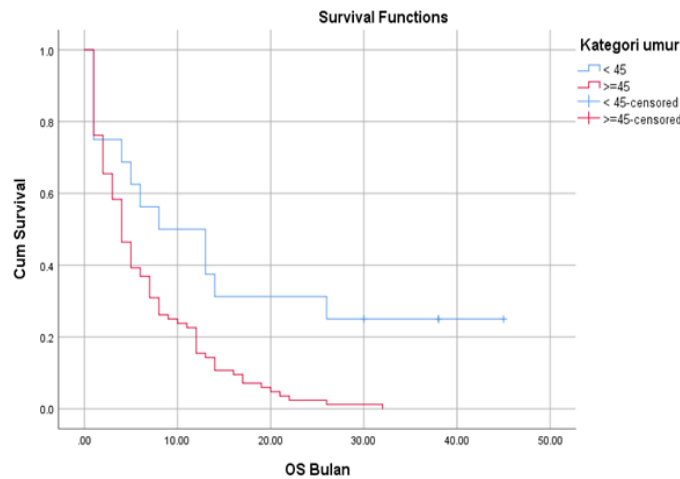
Figure 1. Kaplan-Meier curve of age group to survival
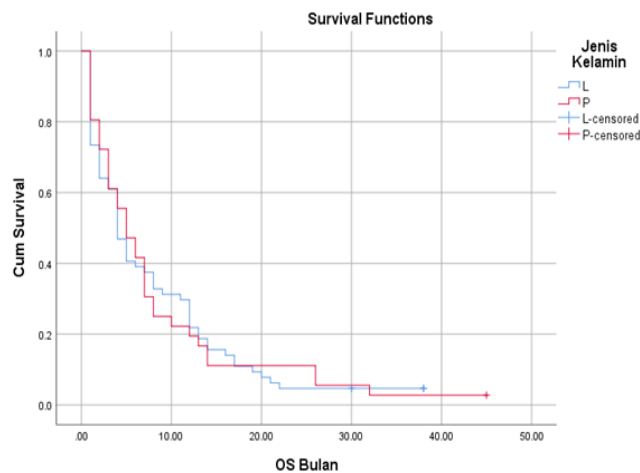
Figure 2. Kaplan-Meier curve of gender to survival
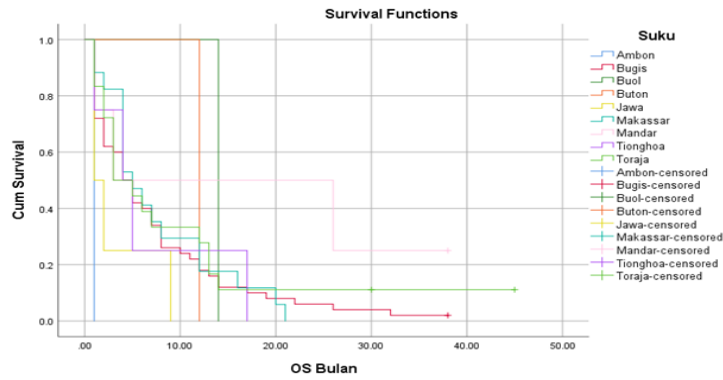
Figure 3. Kaplan-Meier curve of Ethnicity to survival
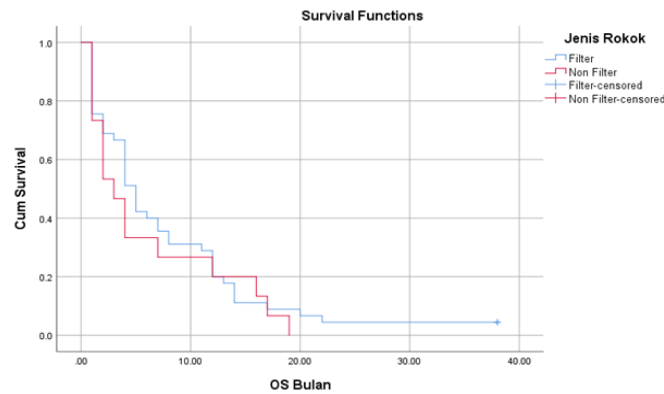

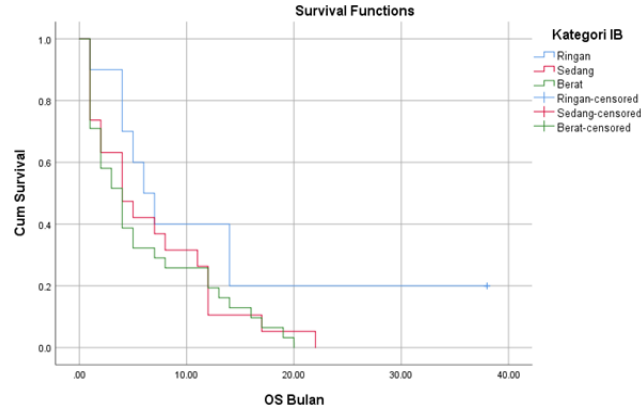**Figure 4. Kaplan-Meier curve of cigarettes on survival**
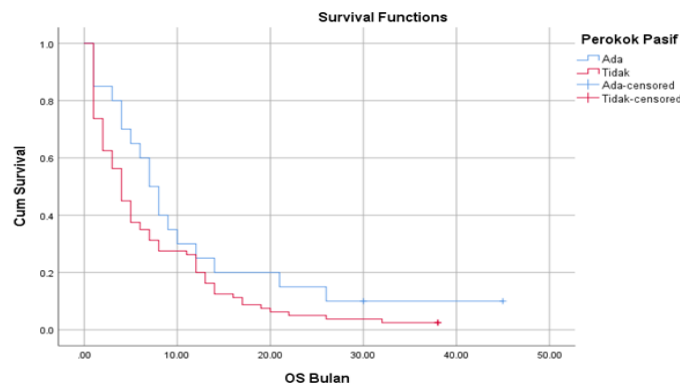

Figure 5. Kaplan-Meier Brinkman index curve for survival

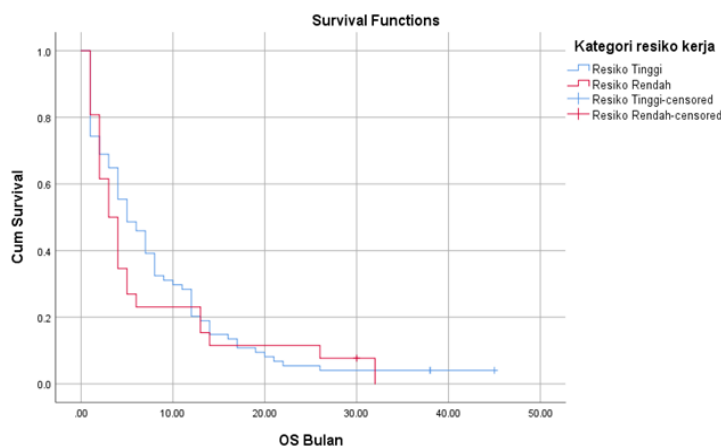**Figure 6. Kaplan-Meier curve of passive smoking on survival**

Figure 7. Kaplan-Meier curve of occupational risk on survival

DISCUSSION

The most age group in this study were 45 years old as many as 84 subjects (84%), and age <45 years 16 subjects (16%). Age 45 years is associated with an increased risk of lung cancer due to continuous shortening of telomeres during repeated cycles of cell replication, and the older a person is, the greater the chance of DNA damage.6 Lung cancer is relatively rare in the younger population, and only less frequently. of 3.5% of lung cancer patients aged <45 years, but research in the last decade has shown an increased incidence of lung cancer at a younger age. (8,9)

Male and female sex had a median survival of 4 and 5 months, although the median survival was better for women, this difference was not statistically significant (p > 0.05). The Australian study by Yu et al. showed that the survival of women with lung cancer was significantly better than that of male subjects. This significant difference was due to differences in histology, stage at diagnosis, treatment, and smoking status.(10)

The tendency to increase adenocarcinoma is influenced by several factors, including the use of cigarettes from high tar to filter cigarettes with low tar in recent years. To compensate for the changing pattern of smoking more frequently and inhalation of cigarettes more deeply, an increase in the number of cigarettes. More intense smoking and deeper inhalation of tobacco smoke and higher delivery of carcinogens such as nitrogen oxides and nitrosated compounds found in greater amounts in filter cigarettes to the periphery of the lung are thought to be the cause of the increased incidence of adenocarcinoma in smokers. (11,12)

There was no significant difference in survival among the rthnicity. Indonesia is a multiethnic country, there are more than 300 different ethnicities in Indonesia. Santoso A and Munawwarah S (2018), studied the proportion of adenocarcinoma in Makassar that reported the proportion of adenocarcinoma was found in 76 samples of men (75.2%) and 25 samples of women (24.5%). They did not find publications on other studies involving ethnic subjects in Sulawesi.(13)

The risk of exposure in the work environment with high and low risk was significant (p = 0.01) with the type of cytology/histology of NSCLC. Occupations with high risk tended to be more with cytologic/histological types of adenocarcinoma (n = 31) and SCC (n = 30). Occupations with a high risk median survival of 5 months, 2 months better than low risk, this happens because the low risk group tends to be diagnosed at an advanced stage (92.3% compared to 90.8% at high risk), also in the low risk group more are not received treatment (42.3% versus 30.3% at high risk). Workers who are exposed to harmful particles, diesel fumes, crystalline silica, arsenic, pesticides increase the risk of lung cancer of all subtypes, with the highest frequency being SCC and Lung Cancer

Types Small Cell Carcinoma and adenocarcinoma with the lowest rates. 104 However, in this study, the highest frequency in high-risk occupations was adenocarcinoma (n=30) and SCC (n=30).

The degree of Brinkman index (BI) based on the type of cytology/histology of NSCLC was found to be significant (p=0.02), with the most severe BI being the type of cytology/histology of adenocarcinoma. There were no significant differences between filter and non-filter cigarettes, passive smokers and non-smokers (p>0.05). Filter cigarettes have a median survival of 5 months, and non-filter 3 months. Although filter cigarettes tended to have a longer median survival, it was not statistically significant (p=0.46).

The low IB category had a longer median survival, ie 6 months, compared to moderate and severe IB at 4 months each, but not statistically significant (p = 0.12). Passive smokers tend to have a better median survival (7 months) than nonsmokers (3 months), but in the non-passive smoker group, more people did not receive treatment (50% compared to passive smokers 23.8%). Research by Kenfield et al., subjects were active smokers or former smokers with histological results of adenocarcinoma (51.1%) and SCC (18.9%).(14) In contrast to the meta-analysis study by Lee et al. found the strongest relationship between smoking and the incidence of SCC, and the weakest relationship with adenocarcinoma.(15)

There was a family history of cancer in 26 subjects (26%), consisting of a family history of lung cancer in 5 subjects (19.3%) and a family history of other cancers in 21 subjects (80.7%). Research by Spitz et al. demonstrated the influence of a family history of cancer on lung cancer risk in patients who had never smoked, former smokers, and current smokers.(16) The Cassidy et al study also showed a significantly increased risk of lung cancer especially for people with a family history of early-onset lung cancer (<60 years).(17)

There was a history of chronic lung disease in 3 subjects (3%) in the form of a history of being diagnosed with Pulmonary Tuberculosis. The cohort study by Yu et al. reported that the incidence of lung cancer was approximately 11 times higher in the cohort of tuberculosis patients than in nontuberculosis subjects.109 In a population-based case-control study of lung cancer in Shanghai involving interviews during 1984-86 with 1,405 cancer patients and 1,495 controls, a significant increase of 50 % in lung cancer risk, adjusted for smoking, was observed among persons with a history of tuberculosis. Among those diagnosed with tuberculosis in the past 20 years, the risk exceeds 2.5 times. (18)

The median survival of Adenocarcinoma, SCC, NOS and Adenosquamous cytology/ histology were 4 months, 4 months, 6 months and 4 months, respectively. The difference in the type of cytology/histology was not significant for survival. Onal et al. investigated the survival analysis of NSCLC patients in Turkey involving 518 patients. Median overall survival was 11.7 months, adenocarcinoma 12.6 months, SCC 11.5 months, other types of NSCLC 8.7 months. There was no significant difference in survival between the histological types studied (p=0.38). Stages IIIb and IIIc had the best median survival (12 and 13 months). Although stages IIIb and IIIc had a better median survival, they were not statistically significant (p = 0.06). Research Onal et al. found the difference in survival between the early and advanced stages, with a p value < 0.001. Median early-stage survival was 16.27 months compared to 8 months for advanced stage. (18)

A study by Onal et al. (2020) included samples at an early stage (43.7%), also the majority were in good performance status (≤ 2 as much as 80.1%). Whereas in our study, the initial sample was only 8.8% and did not get performance status data so that it could obscure the results. Another study showed variations in median survival when given EGFR TKI in NSCLC with EGFR mutations, with a median survival range of

19 – 22.7 months (Erlotinib), 21.6 – 34.8 months (Gefitinib), 22.1 months with Afatinib. Meanwhile, in the subjects who received the platinum doublet, the median survival was between 8 and 10.3 months. Median survival increased when a platinum doublet was added to immunotherapy (Bavacizumab) 12.3 months.(19)

Subjects who received platinum doublet chemotherapy in this study did not receive maintenance therapy that can improve survival. Maintenance therapy is a treatment strategy that has been extensively investigated in NSCLC. Options for maintenance include continuing the initial combination chemotherapy regimen, continuing only single-agent chemotherapy or introducing a new agent. Therapies that have been studied in this setting in randomized trials to date include chemotherapy, molecularly targeted agents and immunotherapeutic approaches. The addition of maintenance therapy can increase survival to 14 months.(20)

CONCLUSION
The median survival rate was greater for the age group 45 years than for the age group 45 years. The group of patients who received TKI and chemotherapy had a greater median survival rate than the group of patients who did not get treatment. Measuring the concentration of carcinogens and pollutants in the living and working environment, assessing other risk factors not included in this study such as certain genetic mutations (chromosomal mutations 6q23-25, tumor suppressor gene p53, cytochrome P450), history of infection. lung infections such as HPV infection and Chlamydial pneumonia, and assessment of PS at diagnosis, comorbidities, and nutritional status with a prospective cohort study are all necessary.

Ethical clearance
Statements of approval, both oral and written, were obtained from all research subjects based on the approval of the Ethics Committee of the Faculty of Medicine, Hasanuddin University No.: 81/UN4.6.4.5.31/PP36/2022.

Study limitations
This research has been attempted as much as possible, but there are still limitations in this study, including; The research design was cross sectional, only studied for a limited time and only to prove the conditions that occurred at the time of the study. This study is a retrospective study, most of the Progression-Free Survival (PFS) data was not obtained so that it could not be analyzed. In addition, incomplete patient data was found and telephone interviews were not possible. The number of subjects in this study was also limited, many risk factors were not measured, such as air pollution levels, types of carcinogens in the workplace, indoor radon levels. Factors affecting NSCLC survival such as comorbidities, nutritional status, location of metastases were also not included in the study data.

Conflict of interest: The author state that there is no conflict of interest for writing this article.

REFERENCES
1. World Health Organization. Globocan world cancer report. The Global Cancer Observatory. 2020. p. 1–2.
2. 2Kementerian Kesehatan Republik Indonesia. Kanker Paru. 2017. p. 15–20.
3. de Groot P, Munden RF. Lung Cancer Epidemiology, Risk Factors, and Prevention. Radiol Clin North Am [Internet]. 2012;50(5):863–76. Available from: http://dx.doi.org/10.1016/j.rcl.2012.06.006
4. Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. Eur Respir J [Internet]. 2016;48(3):889–902. Available from: http://dx.doi.org/10.1183/13993003.00359-2016
5. Alfiyan M. Mitigasi dan pencegahan radon di dalam ruangan. Semin Keselam Nukl 2016. 2016;46-1-46–6.
6. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer:

Epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5):584–94.

7. Liang M, Wang L, Cao C, Song S, Wu F. LncRNA SNHG10 is downregulated in non-small cell lung cancer and predicts poor survival. BMC Pulm Med. 2020;20(1):4–9.

8. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32.

9. Ye T, Pan Y, Wang R, Hu H, Zhang Y, Li H, et al. Analysis of the molecular and clinicopathologic features of surgically resected lung adenocarcinoma in patients under 40 years old. J Thorac Dis. 2014;6(10):1396–402.

10. Yu XQ, Yap ML, Cheng ES, Ngo PJ, Vaneckova P, Karikios D, et al. Evaluating Prognostic Factors for Sex Differences in Lung Cancer Survival: Findings From a Large Australian Cohort. J Thorac Oncol [Internet]. 2022;17(5):688–99. Available from: https://doi.org/10.1016/j.jtho.2022.01.016

11. Hoffmann D, Rivenson A, Hecht SS. The biological significance of tobacco-specific N-nitrosamines: Smoking and adenocarcinoma of the lung. Crit Rev Toxicol. 1996;26(2):199–211.

12. Wynder EL, Muscat JE. The changing epidemiology of smoking and lung cancer histology. Environ Health Perspect. 1995;103(SUPPL. 8):143–8.

13. Santoso A, Munawwarah S. The Higher Prevalence of Epidermal Growth Factor Receptor Mutation in the Male Patients of Lung Adenocarcinoma in Makassar, Indonesia. Am J Respir Crit Care Med. 2018;197.

14. Kenfield SA, Wei EK, Stampfer MJ, Rosner BA, Colditz GA. Comparison of aspects of smoking among the four histological types of lung cancer. Tob Control. 2008;17(3):198–204.

15. Fry JS, Hamling JS, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating FEV1 decline to lung cancer risk. BMC Cancer. 2012;12.

16. Spitz MR, Hong WK, Amos CI, Wu X, Schabath MB, Dong Q, et al. A risk model for prediction of lung cancer. J Natl Cancer Inst. 2007;99(9):715–26.

17. Cassidy A, Myles JP, Van Tongeren M, Page RD, Liloglou T, Duffy SW, et al. The LLP risk model: An individual risk prediction model for lung cancer. Br J Cancer. 2008;98(2):270–6.

18. Zheng W, Blot WJ, Liao ML, Wang ZX, Levin LI, Zhao JJ, et al. Lung cancer and prior tuberculosis infection in Shanghai. Br J Cancer. 1987;56(4):501–4.

19. Barr Kumarakulasinghe N, Zanwijk N Van, Soo RA. Molecular targeted therapy in the treatment of advanced stage non-small cell lung cancer (NSCLC). Respirology. 2015;20(3):370–8.

20. Sellmann L, Fenchel K, Dempke WCM. Improved overall survival following tyrosine kinase inhibitor treatment in advanced or metastatic non-small-cell lung cancer-the Holy Grail in cancer treatment? Transl Lung Cancer Res. 2015;4(3):223–7.

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