IJSCIA

The Relationship Between Neutrophil Lymphocyte Ratio and C-Reactive Protein with Depression and Quality of Life in Non-Small-Cell Lung Cancer Patient

Luh Komang Ayu Widhiaty Karang[1], Ida Ayu Jasminarti Dwi Kusumawardani[1], Ni Ketut Putri Ariani[2], I Gede Ketut Sajinadiyasa[1], Ni Wayan Candrawati[1], Ni Luh Putu Eka Arisanti[1], Ida Bagus Ngurah Rai[1]

[1]Department of Pulmonology and Respiratory Medicine, Prof. I.G.N.G. Ngoerah General Hospital, Faculty of Medicine, Udayana University, Indonesia, 80114

[2]Department of Psychiatry, Prof. I.G.N.G. Ngoerah General Hospital, Faculty of Medicine, Udayana University, Indonesia, 80114

E-mail: ayu.widhiaty@gmail.com; jasminarti@unud.ac.id; mahapavitra@yahoo.com; sajinadiyasa@unud.ac.id; candrawati@unud.ac.id; eka.arisanti@unud.ac.id; idabagus_ngurahrai@unud.ac.id

*Corresponding author details: Ida Ayu Jasminarti Dwi Kusumawardani; jasminarti@unud.ac.id

ABSTRACT

Background: Lung cancer is a global problem and the second most common cancer case for newly diagnosed cancers in 2020. Lung cancer is related to the inflammatory process, and symptoms of depression are often found in lung cancer patients. Improving the quality of life is one of the goals in advanced lung cancer treatment. This study aims to find the relationship between increased inflammatory markers such as neutrophil lymphocyte ratio (NLR), c-reactive protein (CRP) and depression with quality of life in patients with advanced non-small cell lung carcinoma. **Methods:** This was an observational analytic study conducted using a cross sectional design at Prof. Ngoerah Denpasar General Hospital (November 2022-August 2023). Univariate analysis presents data in the form of frequency, mean and standard deviation. Bivariate analysis was performed using the Chi-Square test and multivariate analysis using logistic regression. **Results:** The total samples in this research were 110 samples. The results of bivariate analysis showed that there was a significant relationship between NLR and CRP with depression (OR=3.225, p=0.005; OR=4.645, p=0.001), NLR and CRP with quality of life (OR=4.46, p=0.003; OR=5.313, p<0.001) and depression with quality of life (OR=31.385, p=<0.001). The results of multivariate analysis showed that NLR and CRP are independent risk factors for depression and decreased quality of life in patients with advanced non-small cell lung carcinoma. There was also a significant influence of age on the occurrence of depression (OR=0.364, p=0.037) and the influence of histology type (OR=0.493 p=0.039) on the quality of life of lung cancer patients. **Conclusion:** There was significant relationship between NLR and CRP with depression and quality of life in patients with advanced non-small cell lung carcinoma. Beside inflammatory markers, age is also related to the occurrence of depression and the type of histology influences quality of life.

Keywords: NLR; CRP; depression; quality of life; advanced non-small cell lung carcinoma

INTRODUCTION

Lung cancer is cancer that originates from the parenchymal tissue of the lung or bronchus. Until now, lung cancer is still a global problem. According to Globocan data in 2020 from 19.3 million newly diagnosed cancer cases, lung cancer is the second most common type of cancer after breast cancer in women with an incidence of 2.2 million cases (11.3%). Although ranked second, lung cancer is the highest cause of cancer deaths with 1.7 million deaths (18%) in 2020.

In men, lung cancer is the highest cause of cancer morbidity and mortality, while in women lung cancer is ranked third in cancer incidence after breast cancer and colorectal cancer, and is the second highest cause of mortality after breast cancer [1].

Data in Indonesia states that lung cancer is the most common cancer in men, and the fifth most common cancer in women. From the results of research in various hospitals in Jakarta, lung cancer is the most common case in men, and the fourth most common case in women [2].

Lung cancer in general based on cell of origin is divided into non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). Based on the WHO classification in 2015 the most common types of lung cancer are Adenocarcinoma, squamous cell carcinoma, large cell neuroendocrine carcinoma and carcinoid [3]. Lung cancer is often diagnosed in an advanced stage and severe condition, this is because lung cancer is often asymptomatic in the early stages, mostly affects old age, and lung cancer screening is still rarely carried out in at-risk communities.

In general, the management of advanced lung cancer is palliative, including the provision of chemotherapy and radiotherapy. Nowadays, the management of lung cancer, especially non-small cell lung carcinoma, has evolved with the discovery of various additional treatment modalities such as immunotherapy and targeted therapy [4].

Various new therapeutic modalities are expected to provide an improvement in the survival rate of lung cancer patients, but in reality, the prognosis of lung cancer in general compared to other cancers is still relatively poor. In evaluating the management and treatment of advanced lung cancer, improvement in quality of life is often the targeted end-point [5].

In a study examining quality of life in long-term lung cancer survivors undergoing chemotherapy and radiotherapy found that 67% of patients experienced mild deterioration in global health status, physical and emotional functioning. Conditions such as fatigue, shortness of breath, cough, and financial difficulties ranked the highest on the symptom scale. Quality of life risk factor analysis showed age, exercise, smoking status, and treatment regimen were associated with global health status and functional scores, whereas age, gender, radiation pneumonitis, weight loss, and exercise were associated with symptom scores [6]

Decreased quality of life over time is significantly associated with worsening survival in lung cancer patients with or without targetable driver mutations [7]. There are various factors that affect quality of life in cancer patients including gender, age, smoking status, severity of symptoms, therapy undertaken, intensity of anxiety and depression symptoms, and ability to cope with the disease [8].

One study found that depression in lung cancer patients occurred in 33% of patients before therapy and persisted in more than 50% of patients. Depression is common especially in cancer patients with more severe symptoms or functional limitations [9]. Depression is said to be associated with poorer survival in newly diagnosed non-small cell lung carcinoma patients [10,11]. Patients with depressive symptoms have poorer quality of life, vitality, cancer-specific symptoms, and lower social support than patients without depressive symptoms. The association between depressive symptoms and increased mortality was greater in patients with more lung cancer symptoms or less social support [12].

There are many factors that trigger depression in lung cancer patients, one of which is psychological factors such as death, stress, relationship changes, changes in personal identity and the effects of disease on work, however there are other biological factors that may help explain the high prevalence of depressive symptoms in cancer patients [13]. A biological factor that is widely associated with the occurrence of depression is the high level of inflammation that is often found in lung cancer patients, especially patients with advanced or metastasized lung cancer. Inflammatory mechanisms associated with the risk of lung cancer disease progression may be associated with symptoms of depression that are often experienced by advanced lung cancer patients.

Inflammation and depression that occur in lung cancer patients are associated with a worse prognosis. This is characterized by the discovery of a significant relationship between inflammation and depression with lower survival rates both independently and collectively [14]. Inflammatory cytokines are said to play a role as modulators of the pathogenesis of anxiety and depression. The results of the study found an association between serum TNF-α, IL-1β, IL-6, and IL-17 with an increased risk of anxiety and depression to some extent in patients with non-small cell lung carcinoma[15].

Other inflammatory cytokines such as c-reactive protein (CRP) are widely studied to be associated with an increased risk of mortality in cancer patients, and in lung cancer patients elevated c-reactive protein (CRP) also predicts prognosis as well as helps decide treatment response and identify tumor recurrence [16].

A study by McFarland et al., (2020) found increased CRP levels correlated with the degree of depression (r = 0.47, p < .001). Increased CRP levels > 10 μg/ml are associated with advanced cancer disease and can help diagnose the presence of other accompanying complications. A significant increase in CRP levels > 50-100 μg/ml is associated with advanced disease, metastasis and a poor prognosis [17].

A metanalysis study found that neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and monocyte-lymphocyte ratio were elevated in depressed patients across Chinese subgroups, age and gender. Among the three parameters, it was mentioned that increased neutrophil and lymphocyte ratios were significantly associated with increased risk of depression [18].

The neutrophil lymphocyte ratio in lung cancer patients in the study was found to be significantly associated with the incidence of depression and tended to correlate with anxiety. An increase in lymphocyte neutrophil ratio ≥5 can predict worse survival, and the same results are seen when combined with depression [14].

Until now there have been no studies looking for the relationship between increased inflammatory markers such as neutrophil lymphocyte ratio, c-reactive protein (CRP) and depression with quality of life in patients with advanced non-small cell lung carcinoma at Prof. Dr. I.G.N.G Ngoerah Hospital.

METHOD
Observational research with the design used cross sectional study. This study assessed the quality of life in patients with advanced non-small cell lung carcinoma, at the same time collecting variables related to quality of life. Place: Prof. Dr. I.G.N.G. Ngoerah Hospital. Inclusion criteria: 1) All patients diagnosed with advanced non-small cell lung carcinoma and received services at Prof. Dr. I.G.N.G. Ngoerah Hospital during the period May 2023 - August 2023; 2) Aged ≥18 years; 3) Willing to participate in the study by signing an inform consent. Exclusion criteria: 1) Diagnosed with other malignancies other than non-small cell lung carcinoma; 2) Diagnosed with psychiatric illness before or during suffering f:rom non-small cell lung carcinoma; 3) Diagnosed with an acute infection; 4) Having cognitive function disorders (assessment by filling out the Abbreviated Mental Test/AMT quiz for subjects with elementary school education and below and the Mini Mental State Examination/MMSE questionnaire for subjects with education above elementary school). The data that has been collected will be carried out descriptive statistical analysis, comparative analysis of proportions, and multiple regression logistic tests, the whole process of analyzing the data above using the IBM Statistical Product and Service Solutions (SPSS) v.25 program.

RESULT
This study was conducted with a total sample of 117 but because 7 samples did not meet the completeness of the data so that the final results of the samples analyzed were 110 samples. Of the total 110 samples, 64 were male (58.2%) and 46 were female (41.8%). The mean age ranged from 58.54 years old with the youngest age being 39 years old and the oldest being 82 years old with the overall characteristics of the data in Table 1

TABLE 1: Characteristics of Research Subjects.

Characteristics	n (%)
[a] age (years)	
Mean ± standard deviation	58,54 ± 9,772
Age ≥ 60 years	45 (40,9%)
Age < 60 years	65 (59,1%)
Gender	
Male	64 (58,2%)
Female	46 (41,8%)
Education	
Basic-intermediate	95 (86,4%)
High	15 (13,6%)
Jobs	
Work	91 (82,7%)
Not working	19 (17,3%)
Smoking status	
Smoking	39 (35,5%)
No smoking	71 (64,5%)
Nutritional status	
Skinny	31 (28,2%)
Normal	79 (71,8%)
Performance status (PS)	
ECOG >2	6 (5,5%)
ECOG ≤ 2	104 (94,5%)
Histology Type	
Non-squamous lung carcinoma	80 (72,7%)
Squamous lung carcinoma	30 (27,3%)
Adenosquamous carcinoma	12 (10,9%)
Squamous cell carcinoma	18 (16,4%)
Cancer stage	
IIIB	6 (6,4%)
IIIC	6 (1,8%)
IVA	67 (60,9%)
IVB	34 (30,9%)

Characteristics	n (%)
Comorbid diseases	
Without comorbidities	70 (63,6%)
With comorbidities	40 (36,4%)
1 comorbid	27 (24,5%)
2 comorbidities	9 (8,2%)
3 comorbidities	4 (3,6%)
Type of treatment	
No therapy yet	38 (34,5%)
Already in therapy	71 (65,5%)
Chemotherapy	40 (36,4%)
Targeted therapy	27 (24,5%)
Targeted therapy + chemotherapy	2 (1,8%)
Targeted therapy + radiotherapy	1 (0,9%)
Targeted therapy + chemotherapy + radiotherapy	1 (0,9%)
Chemotherapy + radiotherapy	1 (0,9%)
Neutrophil lymphocyte ratio[b] , median (min-max)	2,9 (0,44-19,62)
Neutrophil lymphocyte ratio ≥4	37 (33,6%)
Neutrophil lymphocyte ratio <4	73 (66,4%)
C-reactive protein (CRP) [b] , median (min-max)	13 (1-318,10)
C-reactive protein (CRP) ≥10 mg/dL	61 (55,5%)
C-reactive protein (CRP) <10 mg/dL	49 (44,5%)
BDI Score	
Depression	37 (33,6%)
Not depressed	73 (66,4%)
Quality of Life	
Bad	75 (68,2%)
Good	35 (31,8%)

Notes: ECOG (Eastern Cooperative Oncology Group), BDI (The Beck Depression Inventory),[a] Normally distributed data,[b] Non-normally distributed data.

The results of bivariate analysis of the independent variable neutrophil-lymphocyte ratio and the dependent variable depression are shown in Table 2.

The neutrophil-lymphocyte ratio obtained an odds ratio of 3.225 with a 95% confidence interval (95% CI) in the range of 1.398-7.441 (p value = 0.005).

TABLE 2: Relationship between neutrophil-lymphocyte ratio and depression.

Neutrophil-lymphocyte ratio	Depression		P-value	OR (95% CI)
	Yes	No		
≥4	19 (51,4%)	18 (48,6%)	0,005	3,225 (1,398-7,441)
<4	18 (24,7%)	55 (75,3%)		

Bivariate analysis to find the association of CRP with depression found that 29 patients (47.5%) with high CRP ≥10 had depression and 31 patients (52.5%) did not have depression, as shown in Table 3.

The odds ratio of the association of CRP with depression was 4.645 with 95% CI in the range of 1.871-11.528 (p value = 0.001).

TABLE 3: Relationship between CRP and depression.

CRP (mg/dL)	Depression		P-value	OR (95% CI)
	Yes	No		
≥10	29 (47,5%)	32 (52,5%)	0,001	4,645 (1,871-11,528)
<10	8 (16,3%)	41 (83,7%)		

The quality of life in this study was assessed with the EORTC QLQ-C30 questionnaire, the results of global health status scale were converted into a score of 0-100, where the quality of life was poor if the value was <70, and the quality of life was good ≥ 70.

In bivariate analysis, it was found that patients with a high neutrophil lymphocyte ratio ≥4 as many as 32 people (86.5%) had a poor quality of life and 5 people (13.5%) had a good quality of life. Meanwhile, 43 people (58.9%) with a low neutrophil lymphocyte

ratio <4 had a poor quality of life and 30 people (41.1%) had a good quality of life. Odds ratio of the relationship between neutrophil lymphocyte ratio and quality of life was 4.46 with 95% CI in the range of 1.560-12.779 (p value = 0.003). The results of the analysis are shown in Table 4.

TABLE 4: Relationship between neutrophil lymphocyte ratio and quality of life.

Neutrophil Lymphocyte Ratio	Quality of Life		P-value	OR (95% CI)
	Bad	**Good**		
≥4	32 (86,5%)	5 (13,5%)	0,003	4,46 (1,560-12,779)
<4	43 (58,9%)	30 (41,1%)		

Bivariate analysis of CRP variables with quality of life found that patients with high CRP levels ≥10 mg/dL, namely 51 people (83.6%) had a poor quality of life and as many as 10 people (16.4%) had a good quality of life. While 24 people (49%) with low CRP levels <10 mg/dL had poor quality of life and 25 people (51%) with good quality of life.

From this analysis, it was found that CRP was associated with the quality of life of non-small cell lung carcinoma patients with an odds ratio of 5.313 at 95%CI in the range of 2.205-12.799 (p value <0.001). The results of the analysis are shown in Table 5.

TABLE 5: Relationship between CRP and quality of life.

CRP (mg/dL)	Quality of life		P-value	OR (95% CI)
	Bad	**Good**		
≥10	51 (83,6%)	10 (16,4%)	<0,001	5,313 (2,205-12,799)
<10	24 (49%)	25 (51%)		

In addition to finding the relationship between the independent variables of lymphocyte neutrophil ratio and CRP, the relationship between depression as the independent variable and quality of life as the dependent variable was also sought. From the analysis, it was found that of the 37 patients who experienced depression, a total of 36 people had a poor quality of life (97.3%) and only 1 person (2.7%) had a good quality of life.

Whereas from 73 people who did not experience depression, 39 people (53.4%) had a poor quality of life and the remaining 34 people (46.45) had a good quality of life. The relationship between depression and quality of life has an OR of 31.385 with 95%CI in the range of values 4.083-241.251 (p value <0.001) (Table 6).

TABLE 6: Relationship between depression and quality of life.

Depression	Quality of life		P-value	OR (95% CI)
	Bad	**Good**		
Yes	36 (97,3%)	1 (2,7%)	<0,001	31,385 (4,083-241,251)
No	39 (53,4%)	34 (46,4%)		

The next analysis in this study is multivariate analysis which aims to determine the relationship between neutrophil lymphocyte ratio and CRP, as well as confounding variables with depression and quality of life. Logistic regression multivariate analysis

was performed to assess and prove the strength of the relationship of each independent variable as a risk factor for depression and decreased quality of life in patients with advanced non-small cell lung carcinoma after controlling for confounding variables in the analysis Table 7.

TABLE 7: Results of multivariate logistic regression analysis of depression.

Variables	OR	95% CI	P-value
Age	0,364	0,141-0,941	0,037*
Education	4,153	0,757-22,786	0,101
Neutrophil Lymphocyte Ratio	2,599	1,015-6,659	0,047*
CRP levels	3,781	1,410-10,142	0,008*

Description: CRP (c-reactive protein)
*Has a significant effect (p value <0.05)

Based on the results of multivariate logistic regression analysis in Table 7, it was found that the ratio of neutrophil lymphocytes, CRP levels, and age influenced the occurrence of depression in patients with advanced non-small cell lung carcinoma with OR values of 2.599 (95% CI 1.015-6.659; p value = 0.047) for neutrophil lymphocyte ratio, 3.781 (95% CI 1.410-10.142; p value = 0.008) for CRP levels, and 0.364 (95% CI 0.141-0.941; p value = 0.037) for age variables.

When bivariate analysis was conducted for the age variable with depression, it was found that there was a difference in the incidence of depression in both age groups but the difference was not significant (OR 2.61; p value = 0.09 with 95% CI 0.888-4.781) (table 8). So that the results of the multivariate results can be concluded that when the neutrophil-lymphocyte ratio ≥4 and CRP levels ≥10, the age factor < 60 years increases the patient's risk of depression compared to the age group ≥ 60 years.

TABLE 8: Relationship between age and depression.

Age (year)	Depression		P-value	OR (95% CI)
	No	**Yes**		
≥60	34 (75,6%)	11 (24,4%)	0,090	2,061 (0,888-4,781)
<60	39 (60,0%)	26 (40,0%)		

Judging from the coefficient of determination shows $R^2 = 0.263$, it can be interpreted that the ratio of neutrophil lymphocytes, CRP levels and age can explain or contribute to the occurrence of depression in non-small cell lung carcinoma patients in 26% of cases.

Whereas the results of multivariate analysis for quality of life found that neutrophil lymphocyte ratio, CRP levels, and histology type factors were associated with quality of life, where the histology type of adenocarcinoma or non-squamous lung carcinoma had a lower chance of decreasing quality of life than the histology type of squamous lung carcinoma (adenosquamous carcinoma or squamous cell carcinoma). Lymphocyte neutrophil ratio, CRP level and histology type were significantly associated with quality of life with OR of 3.645 (95% CI 1.142-11.638; p value = 0.029) for lymphocyte neutrophil ratio, 4.327 (95% CI 1.659-11.289; p value = 0.003) for CRP level and 0.493 (95% CI 0.252-0.966; p value = 0.039) for histology type, respectively. The multivariate analysis table for quality of life variables can be seen in Table 9.

TABLE 9: Results of multivariate logistic regression analysis of quality of life.

Variables	OR	95% CI	P-value
Age	0,393	0,152-1,016	0,054
Histology type	0,493	0,252-0,966	0,039*
Neutrophil Lymphocyte Ratio	3,645	1,142-11,638	0,029*
CRP levels	4,327	1,659-11,289	0,003*

Description: CRP (c-reactive protein)
*Has a significant effect (p value <0.05)

When bivariate analysis was conducted to find the relationship between histology type and quality of life, it was found that there was a significant relationship between the two, where the type of non-squamous cell lung carcinoma had a 4 times chance of experiencing a good quality of life than the histology type of squamous cell lung carcinoma with OR 4.112 p value = 0.010 at 95% KI in the range of 1.309-12.919 (Table 10).

Judging from the coefficient of determination shows $R^2 = 0.312$, it can be interpreted that the ratio of neutrophil lymphocytes, CRP levels and histology type can explain the occurrence of poor quality of life in non-small cell lung carcinoma patients in 31% of cases.

TABLE 10: Relationship between histology type and quality of life.

Histology Type	Quality of life		P-value	OR (95% CI)
	Bad	**Good**		
Non-Squamous	31 (38,8%)	49 (61,3%)	<0,011	4,112 (1,309-12,919)
Squamous	4 (13,3%)	26 (85,7%)		

DISCUSSION

The worldwide incidence of lung cancer is estimated at 2.2 million cases. In Indonesia alone, according to GLOBOCAN data, the estimated incidence rates up to 5 years is 946 thousand people. This study data obtained a total of 110 patients with advanced non-small cell lung carcinoma who underwent treatment at the pulmonary polyclinic of Prof. I.G.N.G. Ngoerah Hospital during the time period May - August 2023. Of the 110 people who became research subjects 58.2% were male with an average age of 58.54 ± 9.772. This finding is in line with previous research conducted at Prof. I.G.N.G. Ngoerah Hospital which found 63.5% were male and had an average age of 57.70 ± 9.86 [19,20].

Historically, the incidence of lung cancer is more common in men than women with an average age of 60 years (Chen, et al., 2015). From a large-scale study conducted in France found 65.4% of lung cancers occurred in men with an average age at diagnosis of 67.8 ± 10.3 years. It was also found that there was a shift in patterns over the past 2 decades where there was a significant increase in the proportion of lung cancer incidence in women [21].

However, in Indonesia, lung cancer is still the most common cancer in men and the fifth most common of all cancers in women. Compared to women, men in general tend to start smoking at a younger age, smoke more cigarettes per day and with longer smoking duration, smoke deeper cigarettes, and consume cigarettes that contain more tar. Whereas it is known that almost 80% of the incidence of lung cancer in the world is associated with cigarette exposure [5].

In addition, exposure to carcinogens such as air pollution, radon, asbestos, arsenic, silica in the living environment or workplace can also be a risk factor for lung cancer (Pass, et al., 2010). However, the study found that the therapeutic response of lung cancer patients in women was better than men (42% vs. 40%, p = 0.01) and longer survival than men (median OS 9.6 vs. 8.6 months, p = 0.002) [22].

Judging from the age factor, the risk of experiencing lung cancer generally increases with age. This is associated with the process of lung cancer which is a complicated biological process and requires a certain period of time. The aging process is thought to strongly influence the occurrence of lung cancer, such as DNA repair disorders, genomic instability, DNA methylation, cellular damage and aging, inflammation, telomere shortening, immunosenescent, oxidative stress and others [23]. In addition, cancer risk in older populations is also associated with greater accumulation of carcinogen exposure at this age, increased risk of chronic lung disease or infections that trigger inflammation and gene mutations.

In this study, it was found that most of the subjects were working or had worked as much as 82.7% and the rest had never worked or were housewives. This result resembles the findings of a previous study where only 28% were housewives and the rest worked either as farmers, construction laborers, private workers or government workers [19]. However, another study in Daka found that 53.8% of lung cancer patients there did not work [24].

This happened because the sample in this study was dominated by male gender where the role of head of the household and also as the backbone of the family was carried out by men. However, many female patients also worked in this study. The type of work is said in studies related to lung cancer outcomes especially related to mortality rates. The study by Bovio, et al., (2022) found that the survival rate of lung cancer patients varied for each type of occupation with a certain level of skill, where occupations that require the lowest level of skill have the lowest survival in both men and women [25].

Based on the level of education, the study subjects were dominated by a group of patients who never went to school or received primary to secondary education with a case percentage of 86.4%. This finding is in line with the results of a previous study which found that only 9.4% of lung cancer patients received higher education [19]

Another study found that 30.8% of lung cancer patients had higher education (Alam, et al., 2020). The difference in the region where the study took place caused this difference where in Bangladesh there is a higher level of education than the average area in Bali. A study found that higher education levels were positively associated with the quality of life of lung cancer patients before diagnosis both mentally and physically[26].

Most of the study subjects were non-smokers with a case percentage of 64.5%. The same thing was found in previous studies where as many as 68.8% of lung cancer patients did not smoke [20]. Likewise, it was found in research in other areas, namely 51.6% of lung cancer patients never smoked [24]

Worldwide, it is found that 15-20% of men with lung cancer do not smoke and 50% of women do not smoke, of which 60-80% of women with lung cancer who do not smoke occur in Asia. The cause of this phenomenon is still unknown, but there are several things that can be risk factors for lung cancer in non-smoking groups, including age, passive exposure to cigarette smoke, exposure to carcinogens from the environment, exposure to radon substances, genetics, previous history of lung disease, and hormonal factors [27].

Based on nutritional status, 71.8% of research subjects had normal nutritional status. The same results were also found in a previous study where the average BMI of lung cancer patients was 21.08 ± 3.59 (Ekaruna, et al., 2021). Nutritional status is said to correlate with the quality of life of lung cancer patients, where research has found that low nutritional status is a determining factor for poor quality of life in lung cancer patients [8].

The physical appearance status in this study found that most had a good appearance with an ECOG score ≤ 2 (94.5%). While previous research found that 68.8% had an ECOG score ≤ 2 (Andikayasa, et al., 2022). ECOG scores are said to correlate with the quality of life of lung cancer patients, where low quality of life with clinically significant symptom incidence is found more in patients with poor physical appearance compared to good ones [28].

The dominant histology type in this study was adenocarcinoma as much as 72.7%, followed by squamous cell carcinoma as much as 16.4% and the remaining type of Adenosquamous carcinoma 10.9%. The same thing was found from previous research, namely 83.8% were adenocarcinoma types, 13.8% were squamous cell carcinoma types, and 2.5% were other types [20]. In general, in the world, the adenocarcinoma type is the most common histological type of non-small cell lung carcinoma with up to 40% of all non-small cell lung carcinoma cases.

The histologic type of lung cancer is associated with lung cancer prognosis, with non-small cell lung carcinoma generally having a better prognosis than small cell lung cancer. Studies to date have found mixed results as to which type of non-small cell lung cancer has a better prognosis. Some studies have found adenocarcinoma types to have a better prognosis but other studies have found squamous cell carcinoma to be better [29].

Lung cancer is generally asymptomatic in the early stages so that in most cases it is diagnosed at an advanced stage. Especially in Indonesia where lung cancer screening programs in at-risk populations are still rarely carried out, so the incidence of lung cancer in Indonesia is dominated by advanced lung cancer. The same thing was found in this study where the most common stage found was the IVA stage as many as 67 (60.9%). The same thing was also found in a previous study where 51.2% of cases were IVA stage [20]

Most of the study sample did not have comorbid diseases, namely 70 people (63.6%), the rest with one comorbid 24.5%, two comorbid 8.2% and three comorbid 3.6%. Another study in China found the same thing where 67.8% of lung cancer patients did not have comorbidities. The results of the study found that comorbidities were positively correlated with an increased risk of hospital readmission within 31 days as well as in-hospital mortality [30].

The number of samples who had not started therapy in this study was 38 people (34.5%), almost comparable to the number who received therapy in the form of chemotherapy, namely 40 people (36.4%). A total of 27 people received target therapy (24.5%) and few received combination or multimodality therapy, namely 2 people (1.8%) received target therapy and continued chemotherapy, and the rest received another multimodality. Previous research found similar results with the proportion of lung cancer patients who had not received therapy as much as 42.4% and received chemotherapy as much as 27.5% [20]Meanwhile, another study found that as many as 53% with first-line treatment [31].

This study found the incidence of depression in advanced stage LCC patients as much as 33.6%. The same thing was also obtained from research by Gonzalez-Ling, et al., (2023), namely as many as 31% of lung cancer patients suffered from depression [31]. Another study found that depression in lung cancer patients occurred in 33% of patients before therapy and persisted in more than 50% of patients. Depression is common especially in cancer patients with more severe symptoms or functional limitations [9]. Depression is said to be associated with poorer survival in newly diagnosed non-small cell lung carcinoma patients [10,11].

The quality of life of non-small cell lung carcinoma patients in this study was found to be 68.2% having a poor global quality of life status with a value limit of < 70%. Similar results were found in a previous study which also examined the quality of life of patients with advanced stage CPSC, as many as 55% of patients experienced poor quality of life [20]. The decline in quality of life over time is significantly associated with worsening survival of lung cancer patients with or without targetable driver mutations [7].

This study found that the neutrophil lymphocyte ratio with depression in non-small cell lung carcinoma patients had a significant relationship, with the calculation of the risk estimate of the neutrophil lymphocyte ratio obtained an odds ratio of 3.225 with a 95% confidence interval (95%CI) in the range of 1.398-7.441 (p value = 0.005). The same results were also found in a study by McFarland, et al., (2020) where NLR was said to be associated with depression (r value = 0.21, p = 0.03), and remained associated after controlling for age, gender and marital status. Increased NLR predicts poor survival in lung cancer patients.

A study looking at the association between systemic inflammation ratio and survival in patients with non-small cell lung cancer found that after adjusting for covariates (ECOG, age, education level, smoking status, and type of therapy) an increase in NLR at diagnosis increased the risk by 2 times to die at a time compared to those without an increase in NLR (HR 1.91; 95% CI 1.29-2.84; p value = 0.001). Patients with baseline NLR > 5 had a 1-year survival estimate of 0.76 (95% CI 0.37-0.57; p value = 0.57). The log rank test obtained significant results (p = 0.001) indicating a difference in survival [32].

The specific molecular mechanisms affecting NLR in cancer are still not fully understood. However, the imbalance between neutrophils and T cells in cancer may occur due to neutrophil-mediated suppression of T cells [33]. Granulocyte-colony stimulating factor (G-CSF) secreted by the tumor or TME causes proliferation of leukocytes (including neutrophils), as well as myeloid-derived suppressor cells (MDSCs) from the bone marrow.

MDSCs suppress the proliferation and expansion of lymphocytes thereby increasing the neutrophil-lymphocyte ratio. Increased NLR is associated with disease progression, while MDSCs directly contribute to cancer progression and metastasis. Progression and metastasis in lung cancer tend to increase patient symptoms and complaints and may influence the occurrence of depression in lung cancer patients.

This study found that 29 patients (47.5%) with high CRP ≥10 experienced depression and 31 patients (52.5%) did not experience depression, so it can be said that CRP has a significant relationship with depression, Odds ratio of 4.645 (95%CI 1.871-11.528; p value = 0.001). These results are similar to research by McFarland, et al., (2020) where increased CRP levels correlate with the degree of depression (r = 0.47, p < .001), where CRP has a moderate level of accuracy in predicting the incidence of depression. The cut-off value of CRP ≥ 3 mg/dL has a sensitivity of 50% and specificity of 80%.

In cancer patients, the increase in CRP levels is triggered by platelet recruitment and fibrin accumulation in tissues damaged by cancer cells, resulting in an acute inflammatory response. If the inflammatory trigger cannot be overcome, a chronic excessive inflammatory response will occur. Continuous oxidative stress and cytokine production by activated macrophages and neutrophils increase tumorigenicity in epithelial cells, causing further epithelial-to-mesenchymal transition (EMT).

Excessive cytokine release (e.g., IL-6) from the TME increases pCRP production by hepatocytes. pCRP secretion and mCRP-dependent inflammatory signaling (e.g., in endothelial cells and engaged neutrophils), as well as its direct action on the ECM, contribute to tumor progression through ROS and cytokine signaling in the TME [17].

Elevated CRP levels in cancer patients are a marker of increased inflammation, where chronic inflammation in the body will consistently affect the basal ganglia, cortex, and motor pathways to reduce motivation and motor activity. Increased inflammatory cytokines are associated with increased oxidative stress and the formation of reactive oxygen and reactive nitrogen species (ROS and RNS). Increased ROS and RNS contribute to oxidizing tetrahydrobiopterin (BH4) which is a factor required for the enzymatic synthesis of monoamines via phenylamine hydroxylase (PAH), tripthopan hydroxylase (TPH), and tyrosine hydroxylase (TH), thus disrupting the synthesis of serotonin (5-HT), dopamine (DA), and norepinephrine (NE) due to the low availability of monamines (trypthopan and tyrosine) as serotonin and dopamine precursors. Low serotonin, dopamine and norepinephrine can then lead to depressive symptoms [34].

This study found a significant association between the neutrophil-lymphocyte ratio and the quality of life of advanced non-small cell lung carcinoma

patients with an OR of 4.46 with an CI of 95% in the range of 1.560-12.779 (p value = 0.003). The neutrophil-lymphocyte ratio is widely studied and associated with the prognosis of lung cancer patients. As a previous study found that a neutrophil lymphocyte ratio >3.37 was associated with 1-year survival of advanced non-small cell lung carcinoma patients [19]. Another study found a high neutrophil lymphocyte ratio as an independent factor for poor prognosis in non-small cell lung carcinoma patients who had not started therapy, with a cutoff value of NLR ≥ 5 [35].

Although there have been no studies assessing the direct relationship of NLR with the quality of life of advanced non-small cell lung carcinoma patients, NLR has been widely known to be associated with cancer patient outcomes, especially lung cancer patients. From the results of a metaanalysis looking for the association of NLR with overall survival (OS) and progression-free survival (PFS) in lung cancer patients found that NLR values before starting therapy predicted poor OS with Hazard ratio (HR 1.45 95%CI 1.30-1.64) and poor PFS (HR1.42 95%CI 1.15-1.74). Subgroup analysis showed the prognostic value of NLR in predicting poor OS was increased in patients undergoing surgery, and early stage disease. The cutoff value of NLR ≥4 was significant as a predictive value of poor OS and PFS [36].

An increase in neutrophil-lymphocyte ratio results from lymphopenia or an increase in neutrophils and monocytes. Lymphocytes play an important role in cell-mediated antitumor immune responses in various cancers. CD8+ T cells can control tumor growth through cytotoxic activity and induce apoptosis of tumor cells. On the other hand, neutrophils increase in cancer patients due to the production of paraneoplastic myeloid growth factor by cancer cells themselves. In addition, an increase in neutrophils can also occur due to bacterial co-infection or cancer-related inflammation [35].

A high neutrophil lymphocyte ratio in cancer patients is associated with lung cancer progression and metastasis. Research by Hu C. et al., (2022) found a positive correlation between NLR levels and brain metastases in non-small cell lung carcinoma patients, where an increase in NLR was significantly associated with an increased risk of brain metastases, especially in female patients and with adenocarcinoma histology type [37].

Another study found a relationship between NLR levels and the risk of lung cancer recurrence, where NLR> 4.08 increases the risk of lung cancer recurrence and worsening OS (Abigail C. et al., 2021). NLR levels are also said to be useful for determining the prognosis of lung cancer patients, one of which is median survival time, where patients with NLR < 3 have a better medial survival time (31.1 months) compared to NLR levels ≥ 3 (18 months) [38].

This study found that in patients with advanced non-small cell lung carcinoma, CRP levels ≥ 10 mg/dL had

a 5 times risk of experiencing poor quality of life with an odds ratio of 5.313 at 95% CI in the range of 2.205-12.799 (p value <0.001). Increased CRP levels as one of the markers of systemic inflammatory response was found to be not significantly associated with quality of life as seen from the EORTC QLQ-C30 subscale score based on research by Scott HR. et al., (2002), but was associated with greater weight loss, worsening physical appearance status, more fatigue and worsening survival in patients with advanced non-small cell lung carcinoma [39].

There are not many studies that look for the relationship between CRP and the quality of life of lung cancer patients, however many studies have proven CRP as a predictor of prognosis in cancer patients including lung cancer. From a metanalysis data by Shrotriya S. et al., (2015) found 24 studies that examined CRP as a predictor of lung cancer prognosis, where 22 studies proved CRP was associated with the prognosis of lung cancer patients, while 2 studies found CRP not as a predictor factor, and 2 other studies found CRP as a predictor factor only in univariate analysis [16].

This is in accordance with the results of another study by Hotta T. et al., (2020) which found that high CRP levels predicted an unfavorable therapeutic response and became a significant negative prognostic factor for OS in patients with advanced non-small cell lung carcinoma with or without epidermal growth factor receptor (EGFR) mutations [40].

CRP is an inflammatory marker, an acute phase protein that is synthesized in the liver in response to various inflammatory stimuli. CRP consists of 5 identical subunits that form a planar ring that makes the protein stable. CRP can bind to a variety of exogenous and endogenous ligands that are exposed on the cell membrane in the presence of damage, necrosis or apoptotic cells. CRP strongly activates the classical complement pathway which further amplifies tissue damage and potentially makes the disease more severe [41].

CRP dissociates into monomeric CRP (mCRP) at the endothelial cell membrane, where mCRP increases tissue factor (TF) expression and triggers angiogenic effects and triggers angiogenesis. In addition, CRP can also affect various signaling molecules on macrophages and monocytes that affect their function. CRP was found to interact with Toll like receptor (TLR) which is a receptor that recognizes PAMPs or DAMPs on the cell surface, triggering an innate immune response. CRP interacting with TLRs leads to signaling pathways that increase the production of pro-inflammatory cytokines including TNF-α, IL-1, and IL-6 in macrophages and monocytes. These cytokines cause further tumor growth, angiogenesis, tumor cell survival, proliferation, and tumor cell resistance to apoptosis [41]. This process will trigger further cancer progression and metastasis, and indirectly affect the increase and worsening of patient symptoms and complaints and may risk contributing to reducing the quality of life of lung cancer patients.

The relationship between depression and quality of life has a strong relationship, namely lung cancer patients who are depressed are 31 times more likely to experience poor quality of life than those who are not depressed, with OR 31.385 (95%CI in the range of values 4.083-241.251; p value <0.001). Similar results were also found by Khue PM. et al., (2019) where depression is significantly associated with a decrease in quality of life [42].

Depression and anxiety occur in nearly one-third of patients newly diagnosed with non-small cell lung carcinoma. Depression and anxiety are significantly associated with reduced quality of life and depression itself is independently associated with poor treatment adherence and prognosis [43].

In another study conducted on Coronavirus Disease 19 (COVID-19) patients, depression was found to occur in 43.1% of patients with clinically stable, where patients with depression had a lower quality of life than without depression. The relationship between depression and quality of life has been widely studied before and it is proven that quality of life is closely related to distress factors such as physical and mental stress where depression has an impact on daily life functions so that it has a negative correlation with quality of life. Similar results were also found in different disease population groups such as diabetes patients [44], coronary artery disease [45], and gastrointestinal disease [46].

From the study data, it was found that in addition to depression being associated with a decrease in quality of life, depression detected before starting lung cancer therapy is also at risk of increasing mortality and shortening the survival of lung cancer patients, especially in Asian races. So that when managing lung cancer patients, it is also expected to pay attention to the emotional and psychological state of patients in order to provide good therapeutic effects for patients.

From the results of multivariate analysis to determine the effect of covariates on the pure relationship of inflammatory markers neutrophil lymphocyte ratio and CRP with depression, it was found that neutrophil lymphocyte ratio and CRP were still significantly associated with depression, the OR value was 2.599 (95% CI 1.015-6.659; p value = 0.047) for neutrophil lymphocyte ratio, 3.781 (95% CI 1.410-10.142; p value = 0.008) for CRP levels. Lymphocyte neutrophil ratio and CRP are independent risk factors for depression in patients with advanced non-small cell lung carcinoma.

However, in addition to the neutrophil lymphocyte ratio and CRP, it turns out that the age factor also affects the occurrence of depression along with the neutrophil lymphocyte ratio and CRP levels in advanced non-small cell lung carcinoma patients with an OR value of 0.364 (95%CI 0.141-0.941; p value = 0.037), where in the state of high neutrophil lymphocyte ratios and high CRP levels, the increasing age the higher the probability of not experiencing depression.

However, the bivariate analysis between age and depression showed insignificant results, which means that the age variable affects the occurrence of depression only when the neutrophil lymphocyte ratio is ≥ 4 and the CRP level is ≥ 10.

This finding is different from the results of previous studies that found a tendency for depression to occur at an older age, but the difference in the occurrence of depression according to age is also said to be insignificant. The risk of depression is said to be highest in the old adult age group [47].

The incidence of depression by age in the cancer patient population is controversial, some studies have found the risk of depression decreases with age but some studies have also found that depressive symptoms can increase with age [48].

In the general population it is found that depressive symptoms in adulthood follow a U-shape where depressive symptoms increase highest in young adulthood then decrease in middle adulthood and increase again in old adulthood [49]. Depressive symptoms increase highest in young adulthood because at that age range is vulnerable to experiencing intense social stressors but still lacks the ability of the required coping mechanism, and over time the increase in age will lead to increased wisdom in dealing with various problems so as to reduce depressive symptoms in middle adulthood. Whereas in old adulthood depressive symptoms increase again due to the increasing burden of disease, functional limitations, psychological processes, life environment and life events that have a negative impact.

While the results of multivariate analysis for quality of life found that in addition to the ratio of neutrophil lymphocytes and CRP levels, histology type factors are also associated with quality of life, where the histology type of adenocarcinoma or non-squamous cell lung carcinoma has a lower chance of a decrease in quality of life than the histology type of squamous cell lung carcinoma (adenosquamous carcinoma or squamous cell carcinoma). Lymphocyte neutrophil ratio and CRP levels were significantly associated with quality of life with ORs of 3.645 (95% CI 1.142-11.638; p value = 0.029) and 4.327 (95% CI 1.659-11.289; p value = 0.003), respectively. In the setting of high neutrophil ratio and high CRP levels, histology type determined the odds of poor quality of life with an OR of 0.493 (95% CI 0.252-0.966; p value = 0.039). The results of the bivariate study for histology type with quality of life also showed a significant association with an OR value of 4.112 p value = 0.010 at 95% CI in the range of 1.309-12.919.

From several studies it was found that the histology type of adenocarcinoma has a better prognosis than the type of squamous cell carcinoma or small cell carcinoma lung cancer[29,50]. From a study by Wang, et al., (2022) comparing the clinical picture of adenocarcinoma lung cancer with squamous cell carcinoma lung cancer, it was found that squamous cell carcinoma lung cancer has a larger tumor size,

with more severe clinical symptoms including symptoms of cough, fever, and sputum production than adenocarcinoma. In addition, more bacterial and fungal infections were found in squamous cell carcinoma lung cancer with lab results showing higher levels of white blood cells, platelets and kidney function than adenocarcinoma. This suggests that squamous cell carcinoma lung cancer has a more malignant picture than adenocarcinoma [29]

The limitations of this study are: 1) This study did not look for the relationship of personality type, psychological factors, duration of illness to the occurrence of depression; 2) The study only looked at global quality of life and did not further examine the component parts of the quality of life of lung cancer patients that might be influenced or related; 3) This study does not take into account the onset of depressive symptoms whether it starts before cancer diagnosis or after.

This study is the first study to look for the relationship of inflammatory markers, namely the ratio of neutrophils and lymphocytes with depression and quality of life in patients with advanced non-small cell lung carcinoma at Prof. I.G.N.G Ngoerah Hospital.

CONCLUSION
There was significant relationship between NLR and CRP with depression and quality of life in patients with advanced non-small cell lung carcinoma. Beside inflammatory markers, age is also related to the occurrence of depression and the type of histology influences quality of life.

REFERENCES
[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209–49. https://doi.org/10.3322/caac.21660.

[2] Riskesdas. Riset Kesehatan Dasar Nasional. Riskesdas 2018:126.

[3] Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors. Journal of Thoracic Oncology 2015; 10:1243–60. https://doi.org/10.1097/JTO.0000000000000630.

[4] Zingoni A, Fionda C, Borrelli C, Cippitelli M, Santoni A, Soriani A. Natural Killer Cell Response to Chemotherapy-Stressed Cancer Cells: Role in Tumor Immunosurveillance. Front Immunol 2017;8. https://doi.org/10.3389/fimmu.2017.01194.

[5] Pass HI, Carbone DP, Johnson David H., Minna JD. Principles and Practice of Lung Cancer: The Official Reference Text of the International Association for the Study of Lung Cancer (IASLC). vol. 1. 4th ed. UK: Lippincott Williams & Wilkins (LWW). ISBN: 978-0-78-177365-2; 2010.

[6] Ran J, Wang J, Bi N, Jiang W, Zhou Z, Hui Z, et al. Health-related quality of life in long-term survivors of unresectable locally advanced non-small cell lung cancer. Radiation Oncology 2017; 12:195. https://doi.org/10.1186/s13014-017-0909-6.

[7] Billingy NE, Tromp VNMF, van den Hurk CJG, Becker-Commissaris A, Walraven I. Health-Related Quality of Life and Survival in Metastasized Non-Small Cell Lung Cancer Patients with and without a Targetable Driver Mutation. Cancers (Basel) 2021; 13:4282. https://doi.org/10.3390/cancers13174282.

[8] Polański J, Jankowska-Polańska B, Mazur G. Relationship Between Nutritional Status and Quality of Life in Patients with Lung Cancer. Cancer Manag Res 2021; Volume 13:1407–16. https://doi.org/10.2147/CMAR.S287551.

[9] Hopwood P, Stephens RJ. Depression in Patients with Lung Cancer: Prevalence and Risk Factors Derived from Quality-of-Life Data. Journal of Clinical Oncology 2000; 18:893–893. https://doi.org/10.1200/JCO.2000.18.4.893.

[10] Pirl WF, Greer JA, Traeger L, Jackson V, Lennes IT, Gallagher ER, et al. Depression and Survival in Metastatic Non–Small-Cell Lung Cancer: Effects of Early Palliative Care. Journal of Clinical Oncology 2012; 30:1310–5. https://doi.org/10.1200/JCO.2011.38.3166.

[11] Siwik CJ, Cash E, Sephton SE. Depressive symptoms and shorter survival in lung cancer: the role of leukocyte telomere length. Psychol Health 2023; 38:1649–64. https://doi.org/10.1080/08870446.2022.2040500.

[12] Sullivan DR, Forsberg CW, Ganzini L, Au DH, Gould MK, Provenzale D, et al. Depression symptom trends and health domains among lung cancer patients in the CanCORS study. Lung Cancer 2016; 100:102–9. https://doi.org/10.1016/j.lungcan.2016.08.008.

[13] Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the relationship between depression and cancer progression. Int Rev Psychiatry 2014; 26:16–30. https://doi.org/10.3109/09540261.2013.875891.

[14] McFarland DC, Saracino RM, Miller AH, Breitbart W, Rosenfeld B, Nelson C. Prognostic implications of depression and inflammation in patients with metastatic lung cancer. Future Oncology 2021; 17:183–96. https://doi.org/10.2217/fon-2020-0632.

[15] Lázaro S, Pérez-Crespo M, Lorz C, Bernardini A, Oteo M, Enguita AB, et al. Differential development of large-cell neuroendocrine or small-cell lung carcinoma upon inactivation of 4 tumor suppressor genes. Proc Natl Acad Sci U S A 2019; 116:22300–6. https://doi.org/10.1073/pnas.1821745116.

[16] Shrotriya S, Walsh D, Bennani-Baiti N, Thomas S, Lorton C. C-Reactive Protein Is an Important Biomarker for Prognosis Tumor Recurrence and Treatment Response in Adult Solid Tumors: A Systematic Review. PLoS One 2015;10: e0143080. https://doi.org/10.1371/journal.pone.0143080.

[17] Hart PC, Rajab IM, Alebraheem M, Potempa LA. C-Reactive Protein and Cancer—Diagnostic and Therapeutic Insights. Front Immunol 2020; 11:1–17. https://doi.org/10.3389/fimmu.2020.595835.

[18] Huang Y, Ying Z, Quan W, Xiang W, Xie D. The clinical significance of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio in Guillain – Barré syndrome 2018;7454. https://doi.org/10.1080/00207454.2017.1418342.

[19] Andikayasa PM, Suryana K, Dwi Kusumawardani IAJ, Candrawati NW, Arisanti NLPE, Sajinadiyasa IGK, et al. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and one-year survival of lung cancer in Sanglah hospital. International Journal of Advances in Medicine 2022; 9:903. https://doi.org/10.18203/2349-3933.ijam20222096.

[20] Ekaruna IBP, Suryana K, K. JD, Candrawati NW, Arisanti NLPE, Sajinadiyasa IGK, et al. Relationship between anemia, hypoalbuminemia, vitamin D deficiency and quality of life in advanced non-small cell lung carcinoma patients at tertiary hospital in Bali. International Journal of Advances in Medicine 2021; 8:1644. https://doi.org/10.18203/2349-3933.ijam20214126.

[21] Debieuvre D, Molinier O, Falchero L, Locher C, Templement-Grangerat D, Meyer N, et al. Lung cancer trends and tumor characteristic changes over 20 years (2000–2020): Results of three French consecutive nationwide prospective cohorts' studies. The Lancet Regional Health - Europe 2022; 22:100492. https://doi.org/10.1016/j.lanepe.2022.100492.

[22] Wheatley-Price P, Blackhall F, Lee S-M, Ma C, Ashcroft L, Jitlal M, et al. The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials. Annals of Oncology 2010; 21:2023–8. https://doi.org/10.1093/annonc/mdq067.

[23] Berben L, Floris G, Wildiers H, Hatse S. Cancer and Aging: Two Tightly Interconnected Biological Processes. Cancers (Basel) 2021; 13:1400. https://doi.org/10.3390/cancers13061400.

[24] Alam MM, Rahman T, Afroz Z, Chakraborty PA, Wahab A, Zaman S, et al. Quality of Life (QoL) of cancer patients and its association with nutritional and performance status: A pilot study. Heliyon 2020;6: e05250. https://doi.org/10.1016/j.heliyon.2020.e05250.

[25] Bovio N, Grzebyk M, Arveux P, Bulliard J-L, Chiolero A, Fournier E, et al. Work-Related Factors and Lung Cancer Survival: A Population-Based Study in Switzerland (1990–2014). Int J Environ Res Public Health 2022; 19:13856. https://doi.org/10.3390/ijerph192113856.

[26] Schwartz RM, Bevilacqua KG, Alpert N, Liu B, Dharmarajan K V., Ornstein KA, et al. Educational Attainment and Quality of Life among Older Adults before a Lung Cancer Diagnosis. J Palliat Med 2020;23:498–505. https://doi.org/10.1089/jpm.2019.0283.

[27] Dubin S, Griffin D. Lung Cancer in Non-Smokers. Mo Med 2020;117:375–9.

[28] Hensing T, Cella D, Yount S. The impact of ECOG performance status on quality of life symptoms in patients with advanced lung cancer. Journal of Clinical Oncology 2005;23:8099–8099. https://doi.org/10.1200/jco.2005.23.16_suppl.8099.

[29] Wang B-Y, Huang J-Y, Chen H-C, Lin C-H, Lin S-H, Hung W-H, et al. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. J Cancer Res Clin Oncol 2020;146:43–52. https://doi.org/10.1007/s00432-019-03079-8.

[30] Zhu D, Ding R, Ma Y, Chen Z, Shi X, He P. Comorbidity in lung cancer patients and its association with hospital readmission and fatality in China. BMC Cancer 2021;21:557. https://doi.org/10.1186/s12885-021-08272-y.

[31] Gonzalez-Ling A, Galindo Vázquez O, Espinoza Bello M, Robles R, Rascón-Gasca ML, Lara-Mejía L, et al. Quality of life, anxiety, depression, and distress in patients with advanced and metastatic lung cancer. Palliat Support Care 2023;21:608–15. https://doi.org/10.1017/S1478951522001116X.

[32] Andersen BL, Myers J, Blevins T, Park KR, Smith RM, Reisinger S, et al. Depression in association with neutrophil-to-lymphocyte, platelet-to-lymphocyte, and advanced lung cancer inflammation index biomarkers predicting lung cancer survival. PLoS One 2023;18:e0282206. https://doi.org/10.1371/journal.pone.0282206.

[33] Aloe C, Wang H, Vlahos R, Irving L, Steinfort D, Bozinovski S. Emerging and multifaceted role of neutrophils in lung cancer. Transl Lung Cancer Res 2021;10:2806–18. https://doi.org/10.21037/tlcr-20-760.

[34] Felger JC. Imaging the Role of Inflammation in Mood and Anxiety-related Disorders. Curr Neuropharmacol 2018;16:533–58. https://doi.org/10.2174/1570159X15666171123201142.

[35] Kacan T, Babacan NA, Seker M, Yucel B, Bahceci A, Eren AA, et al. Could the Neutrophil to Lymphocyte Ratio be a Poor Prognostic Factor for Non Small Cell Lung Cancers? Asian Pacific Journal of Cancer Prevention 2014;15:2089–94. https://doi.org/10.7314/APJCP.2014.15.5.2089.

[36] Yu Y, Qian L, Cui J. Value of neutrophil-to-lymphocyte ratio for predicting lung cancer prognosis: A meta-analysis of 7,219 patients. Mol Clin Oncol 2017;7:498–506. https://doi.org/10.3892/mco.2017.1342.

[37] Hirsch FR, Spreafico A, Novello S, Wood MD, Simms L, Papotti M. The Prognostic and Predictive Role of Histology in Advanced Non-small Cell Lung Cancer: A Literature Review. Journal of Thoracic Oncology 2008;3:1468–81. https://doi.org/10.1097/JTO.0b013e318189f551.

[38] Ozyurek BA, Ozdemirel TS, Ozden SB, Erdogan Y, Kaplan B, Kaplan T. Prognostic Value of the Neutrophil to Lymphocyte Ratio (NLR) in Lung Cancer Cases. Asian Pac J Cancer Prev 2017;1:1417–21.

[39] Scott HR, McMillan DC, Forrest LM, Brown DJF, McArdle CS, Milroy R. The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. Br J Cancer 2002;87:264–7. https://doi.org/10.1038/sj.bjc.6600466.

[40] Hotta T, Nakashima K, Hata K, Tsubata Y, Isobe T. High serum C-reactive protein levels predict survival in patients with treated advanced lung adenocarcinoma. J Thorac Dis 2021;13:1476–84. https://doi.org/10.21037/jtd-20-3123.

[41] Kim E-S, Kim SY, Moon A. C-Reactive Protein Signaling Pathways in Tumor Progression. Biomol Ther (Seoul) 2023;31:473–83. https://doi.org/10.4062/biomolther.2023.132.

[42] Khue PM, Thom VT, Minh DQ, Quang LM, Hoa NL. Depression and Anxiety as Key Factors Associated With Quality of Life Among Lung Cancer Patients in Hai Phong, Vietnam. Front Psychiatry 2019;10. https://doi.org/10.3389/fpsyt.2019.00352.

[43] Arrieta Ó, Angulo LP, Núñez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martínez-López D, et al. Association of Depression and Anxiety on Quality of Life, Treatment Adherence, and Prognosis in Patients with Advanced Non-small Cell Lung Cancer. Ann Surg Oncol 2013;20:1941–8. https://doi.org/10.1245/s10434-012-2793-5.

[44] Eren İ, Erdi Ö, Şahin M. The effect of depression on quality of life of patients with type II diabetes mellitus. Depress Anxiety 2008;25:98–106. https://doi.org/10.1002/da.20288.

[45] Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive Symptoms and Health-Related Quality of Life. JAMA 2003;290:215. https://doi.org/10.1001/jama.290.2.215.

[46] Sainsbury K, Mullan B, Sharpe L. Reduced quality of life in coeliac disease is more strongly associated with depression than gastrointestinal symptoms. J Psychosom Res 2013;75:135–41. https://doi.org/10.1016/j.jpsychores.2013.05.011.

[47] Linden W, Vodermaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. J Affect Disord 2012;141:343–51. https://doi.org/10.1016/j.jad.2012.03.025.

[48] Avis NE, Levine B, Naughton MJ, Case LD, Naftalis E, Van Zee KJ. Age-related longitudinal changes in depressive symptoms following breast cancer diagnosis and treatment. Breast Cancer Res Treat 2013;139:199–206. https://doi.org/10.1007/s10549-013-2513-2.

[49] Sutin AR, Terracciano A, Milaneschi Y, An Y, Ferrucci L, Zonderman AB. The Trajectory of Depressive Symptoms Across the Adult Life Span. JAMA Psychiatry 2013;70:803. https://doi.org/10.1001/jamapsychiatry.2013.193.

[50] Wang W, Liu H, Li G. What's the difference between lung adenocarcinoma and lung squamous cell carcinoma? Evidence from a retrospective analysis in a cohort of Chinese patients. Front Endocrinol (Lausanne) 2022;13. https://doi.org/10.3389/fendo.2022.947443.