International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 2 | Mar – Apr 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i2.21

# Relationship Between Neutrophil-To-Lymphocyte Ratio, Muscle Mass and Fat Mass Percentage with Quality of Life in Non-Small Cell Lung Cancer

**Ni Nyoman Widyastuti Lestari[1*], Ida Ayu Jasminarti Dwi Kusumawardani[1], Agustinus I Wayan Harimawan[2], Ni Wayan Candrawati[1], I Gusti Ngurah Bagus Artana[1], Ni Luh Putu Eka Arisanti[1], and 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 Clinical Nutrition, Prof. I.G.N.G. Ngoerah General Hospital, Faculty of Medicine, Udayana University, Indonesia, 80114

E-mail: nyoman.widyastuti@gmail.com; jasminarti@unud.ac.id; agustinusharimawan@unud.ac.id; Ignb_artana@unud.ac.id; candrawati@unud.ac.id; eka.arisanti@unud.ac.id; idabagus_ngurahrai@unud.ac.id

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

## ABSTRACT

***Background:*** Cachexia is a challenging condition characterized by the loss of muscle and/or fat mass, often seen in cancer patients. Assessing the impact of inflammatory markers like Neutrophil-to-Lymphocyte Ratio (NLR) along with muscle and fat mass on quality of life can provide valuable insights for improving the management and treatment of patients with non-small cell lung cancer. ***Method:*** This was an analytical observational analytic study conducted using a cross-sectional design in Bali from August to September 2023. Univariate analysis presents data in the form of frequency, median, mean and standard deviation. Bivariate analysis was carried out using Chi-Square and multivariate analysis using multiple logistic regression. ***Result:*** The total research subjects who met requirements were 93 patients. The analysis showed significant relationship between NLR and muscle mass (CI: 95%, OR: 2.373, p value = 0.042) while there was no relationship between NLR and fat mass percentage (CI: 95%, OR: 1.568, p value = 0.382). Variables NLR (CI: 95%, adjOR: 0.217, p value=0.032), muscle mass (CI: 95%, adjOR: 12.207, p value=0.002), fat mass (CI: 95%, adjOR: 9.128, p value =0.020) is significantly related to quality of life. ***Conclusion:*** NLR levels, muscle mass and fat mass percentage have a significant relationship with the quality of life of NSCLC patients. The NLR was related to muscle mass, while there is no relationship between NLR and the percentage of muscle mass.

***Keywords:*** muscle mass, fat mass percentage; quality of life; Neutrophil-to-Lymphocyte Ratio (NLR); Non-Small Cell Lung Cancer (NSCLC)

## INTRODUCTION

Lung cancer is one type of cancer with the largest number of patients. According to data from the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) in 2020, lung cancer ranked second (11.4%) after breast cancer (11.7%) as the most commonly diagnosed cancer worldwide. Lung cancer remains the leading cause of cancer-related deaths, with an estimated 1.8 million deaths (18%) followed by colorectal (9.4%), prostate (9.4%), liver (8.3%), stomach (7.7%), and breast (6.9%) cancers [1].

The ideal diagnosis of lung cancer should be made within two weeks of identifying symptoms, with treatment decisions ideally reached within four weeks [2].

However, several factors contribute to delays in lung cancer therapy, including patient-related factors, diagnostic issues, healthcare system problems, and others. As a result, patients often present at advanced stages with low survival rates and poor quality of life even before therapy begins.

Quality of life plays a crucial role in the management of oncology patients. Assessing a patient's quality of life before therapy provides information about the initial condition of common symptoms and the patient's psychosocial condition, thus serving as prognostic criteria for predicting the patient's response to therapy [3].

The assessment of quality of life provides an insight into how patients perceive the impact of their illness on their well-being and health. The results of this assessment are used to plan interventions aimed at improving patient outcomes [4].

Cancer can lead to a state of chronic inflammation, resulting in the loss of muscle mass and adipose tissue through protein catabolism and fat depletion processes. In cancer patients, there is an increase in protein turnover, decreased protein synthesis, and muscle protein breakdown [5]. Loss of skeletal muscle mass causes weakness and a decrease in functional status, which impairs daily activities in lung cancer patients [6]. The conditions of cachexia and anorexia in cancer patients are associated with risks of hospitalization, activity limitations, depression, and social dysfunction.

Malnutrition screening in cancer patients is crucial. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends screening all cancer patients from the time of diagnosis and conducting it regularly. Examination of muscle and fat mass in patients can be performed using Bioelectrical Impedance Analysis (BIA) equipment. This tool has the advantage of being a non-invasive method that can provide a validated overview of the muscle and body fat composition of cancer patients, and it is recommended in comprehensive cancer management [7-9].

## METHOD

This was an analytical observational analytic study conducted using a cross-sectional design in Bali from August to September 2023.

Inclusion criteria: All patients diagnosed with NSCLC and aged ≥18 years. Exclusion criteria: Having malignancy other than NSCLC, unable to understand research procedure instructions, patients unable to stand, patients with internal electronic devices such as pacemakers and Implantable Cardioverter Defibrillators (ICD), history of amputation, having mental retardation, unwilling to participate in the study. Muscle mass and percentage of fat mass were measured using BIA, Tanita Body Composition Analyzer DC-430MA. Muscle mass is categorized based on the Asian Working Group for Sarcopenia (AWGS) recommendations for Asian populations for BIA with low muscle mass (ASMI < 7 kg/m2 for males and ASMI < 5.7 kg/m2 for females) and high muscle mass (ASMI ≥ 7 kg/m2 for males and ASMI ≥ 5.7 kg/m2 for females) [8]. Quality of life was assessed by completing the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) version 3.0 questionnaire in Indonesian.

Univariate analysis presents data in the form of frequency, median, mean and standard deviation. Bivariate analysis was carried out using Chi-Square and multivariate analysis using multiple logistic regression. The data were analyzed using SPSS software for Windows version 25.0.

## RESULT

The subjects in this study were 93 patients. The majority of research subjects were in the age group of 18-64 years, with 63 patients (67.7%), and the remaining 30 patients (32.3%) were in the age group ≥65 years.

**TABLE 1:** Distribution of subject characteristics.

| Characteristics | n (%) |
|---|---|
| ***Age (years)[a]*** | |
| Mean ± SD | 59,84±10,168 |
| 18-64 years old | 63 (67,7%) |
| ≥ 65 years old | 30 (32,3%) |
| ***Gender*** | |
| Male | 55 (59,1%) |
| Female | 38 (40,9%) |
| ***Education*** | |
| Low -Intermediate | 72 (77,4%) |
| High | 21 (22,6%) |
| ***Employment*** | |
| Working | 47 (50,5%) |
| Not working | 46 (49,5%) |
| ***Marital status*** | |
| Married | 92 (98,9%) |
| Unmarried | 1 (1,1%) |
| ***Performance status (PS)*** | |
| ECOG < 2 | 35 (37,6%) |
| ECOG ≥ 2 | 58 (62,4%) |
| ***Treatment Status*** | |
| On treatment | 72 (77,4%) |
| No treatment | 21 (22,6%) |
| ***Comorbid disease*** | |
| Yes | 19 (20,4%) |
| No | 74 (79,6%) |
| ***Cancer stage*** | |
| IIIB | 6 (6,5%) |
| IIIC | 6 (6,5%) |
| IVA | 59 (63,4%) |
| IVB | 22 (23,7%) |
| ***Histological type*** | |
| Non-small cell lung ***carcinoma*** | 73 (78,5%) |
| Lung adenocarcinoma | 73 (78,5%) |
| Squamous cell lung ***carcinoma*** | 20 (21,5%) |
| Small cell lung ***carcinoma*** | 14 (15,1%) |
| Adenosquamous carcinoma | 6 (6,5%) |

***Notes:*** ECOG (*Eastern Cooperative Oncology Group*), [a]Data is normally distributed

**TABLE 2:** Characteristics of research subjects based on investigated variables.

| Characteristics | n (%) |
|---|---|
| NLR[b], median (min-maks) | 3,22 (0,20-28,87) |
| Low NLR (<3,5) | 51 (54,8%) |
| High NLR (≥3,5) | 42 (45,2%) |
| Muscle mass[a] | |
| Mean ± SD | 4,222±1,112 |
| Low (ASMI <7 kg/m² Male; <5,7 kg/m² Female) | 49 (52,7%) |
| Low (ASMI ≥7 kg/m² Male; ≥5,7 kg/m² Female) | 44 (47,3%) |
| Fat mass percentage[a] (%) | |
| Mean ± SD | 22,783±10,338 |
| Under fat | 22 (23,7%) |
| Normal | 47 (50,5%) |
| Over fat | 24 (25,8%) |
| Quality of life | |
| Poor | 68 (73,1%) |
| Good | 25 (26,9%) |

NLR (*Neutrophil-to-Lymphocyte Ratio*), [a]Data is normally distributed, [b]Data is not normally distributed.

The chi-square test in this study was used to compare the variable of NLR levels as the independent variable with muscle mass as the dependent variable, with the size of their association assessed using odds ratio (OR). In this study, an OR of 2.373 was obtained with a 95% confidence interval [10] of 1.023-5.496 (p-value = 0.042).

**TABLE 3:** The relationship between NLR levels and muscle mass.

| NLR levels | Muscle mass | | *OR* (CI 95%) | *p-value* |
|---|---|---|---|---|
| | Rendah | Tinggi | | |
| High | 27 (64,3%) | 15 (35,7%) | 2,373 (1,023-5,496) | 0,042 |
| Low | 22 (43,1%) | 29 (56,9%) | | |

In this study, NLR levels were compared to the percentage of fat mass in NSCLC patients. The fat mass variable was divided into two groups: underfat and normal-overfat fat mass categories.

The association between NLR levels and fat mass in this study resulted in an OR of 1.568 with a 95% CI ranging from 0.569 to 4.319 (p-value = 0.382).

**TABLE 4:** The relationship between NLR levels and fat mass percentage.

| NLR levels | Fat mass | | | OR (CI 95%)[a] | p-value |
|---|---|---|---|---|---|
| | *Underfat* | Normal | *Overfat* | | |
| High | 14 (33,3%) | 17 (40,5%) | 11 (26,2%) | 1,568 (0,569-4,319) | 0,382 |
| Low | 13 (25,5%) | 30 (58,8%) | 8 (15,7%) | | |

[a]Odds ratio for the occurrence of under fat body mass.

In this study, the NLR levels were compared to the percentage of fat mass in NSCLC patients. The fat mass variable was categorized into two groups: underfat and normal-overfat fat mass categories.

The association between NLR levels and fat mass in this study yielded an OR of 1.568 with a 95% CI ranging from 0.569 to 4.319 (p-value = 0.382).

**TABLE 5:** The relationship between NLR levels and quality of life.

| NLR levels | Quality of life | | *OR* (CI 95%) | Nilai *p* |
|---|---|---|---|---|
| | Poor | Good | | |
| High | 36 (85,7%) | 6 (14,3%) | 3,563 (1,267-10,019) | 0,013 |
| Low | 32 (62,7%) | 19 (37,3%) | | |

In the low NLR group, there were 32 patients (62.7%) with poor quality of life, which was higher than the number of patients with good quality of life, totaling 19 patients (37.3%).

The relationship between the NLR variable and quality of life in this bivariate analysis showed an OR of 4.464 with a 95% CI ranging from 1.267 to 10.019 (p = 0.013).

**TABLE 6:** The relationship between muscle mass and quality of life.

| Muscle mass | Quality of life | | *OR* (CI 95%) | p-value |
|---|---|---|---|---|
| | Poor | Good | | |
| Low | 25 (56,8%) | 19 (43,2%) | 0,184 (0,065-0,520) | 0,001 |
| High | 43 (87,8%) | 6 (12,2%) | | |

In this bivariate analysis, the OR for the relationship between muscle mass and quality of life as shown in Table 5.5 is 0.184 with a 95% CI ranging from 0.065 to 0.520 (p=0.001).

**TABLE 7:** The relationship between fat mass and quality of life.

| Fat mass | Quality of life | | *OR* (CI 95%) | P-value |
|---|---|---|---|---|
| | Poor | Good | | |
| Underfat | 17 (77,3%) | 5 (22,7%) | 1,400 (0,370-5,294) | 0,619 |
| Normal | 34 (72,3%) | 13 (27,7%) | 1,077 (0,363-3,196) | 0,894 |
| Overfat | 17 (70,8%) | 7 (29,2%) | | comparison |

The relationship between fat mass (underfat vs overfat) and quality of life has an Odds Ratio of 1.400 with a 95% CI ranging from 0.370 to 5.294 (p = 0.619). Meanwhile, the relationship between fat mass (normal vs overfat) and quality of life has an Odds Ratio of 1.077 with a 95% CI ranging from 0.363 to 3.196 (p = 0.894). Therefore, it is concluded that there is no association between fat mass and quality of life in this study.

Based on the results of logistic regression analysis in Table 5.8, it was found that NLR levels, muscle mass, fat mass, and performance status variables have a significant relationship with the dependent variable quality of life with a p-value < 0.05. NLR levels have an OR value of 0.217 (95% CI 0.054-0.875; p-value = 0.032), muscle mass has an OR of 12.207 (95% CI 2.504-59.502; p-value = 0.002), fat mass has an OR of 9.128 (95% CI 1.417-58.805; p-value = 0.020), and PS has an OR of 0.139 (95% CI 0.041-0.472; p-value = 0.002). Thus, each variable influences the quality of life of non-small cell lung carcinoma patients in this study.

**TABLE 8:** Results of multivariate logistic regression analysis of quality of life.

| Variable | *adjOR* | CI 95% | p-value |
|---|---|---|---|
| Age | 0,236 | 0,056-1,004 | 0,051 |
| Gender | 3,042 | 0,732-12,641 | 0,197 |
| Education | 1,081 | 0,249-4,696 | 0,918 |
| Employment | 2,466 | 0,567-10,731 | 0,229 |
| *Performance status* (PS) | 0,139 | 0,041-0,472 | 0,002* |
| Treatment status | 1,178 | 0,244-5,684 | 0,839 |
| Comorbid diseases | 0,320 | 0,027-0,647 | 0,178 |
| Cancer stage | 0,790 | 0,120-5,205 | 0,807 |
| Histological type | 0,917 | 0,168-4,997 | 0,912 |
| NLR | 0,217 | 0,054-0,875 | 0,032* |
| Muscle mass | 12,207 | 2,504-59,502 | 0,002* |
| Fat mass | 9,128 | 1,417-58,805 | 0,020* |

## DISCUSSION

Lung cancer remains one of the leading causes of death from cancer worldwide. In Indonesia, the incidence of lung cancer among younger individuals is increasing. This rise may be attributed to genetic factors passed down through generations and influenced by environmental factors such as cigarette smoke, air pollution, asbestos, and exposure to radon gas [11]. Andarini et al. [12] explained that individuals at high risk of lung cancer include those aged >45 years, with a history of smoking or passive smoking, occupational or environmental exposure, and a history of pulmonary fibrosis. Smoking history and types of occupations with occupational and environmental exposure are more commonly found in males. Industrial pollution, and exposure to radon gas, asbestos, and arsenic have synergistic effects with smoking, increasing the risk of lung cancer in males. However, the incidence of lung cancer in females is also increasing. Female lung cancer patients tend to be younger, have a family history of cancer, and are non-smokers [13].

This study aimed to investigate the relationship between NLR levels and muscle mass in NSCLC patients. NSCLC patients with NLR levels ≥3.5 were

found to be 2.373 times more likely to have low muscle mass compared to patients with NLR levels <3.5 (95% CI 1.023-5.496, p-value= 0.042). NSCLC patients with sarcopenia had higher NLR levels (mean NLR = 4.72) compared to patients without sarcopenia (mean NLR = 2.86) (p-value=0.012). Sarcopenia diagnosis in this study was based on low muscle quantity determined by DXA examination (Tenuta et al., 2021). In cancer patients, neutrophil counts were found to increase and have a longer lifespan, which is associated with the Tumor Microenvironment (TME) (Li et al., 2020). Pro-inflammatory cytokines such as IL-6, TNF-α, TGF-β, and IFN-ɤ increase in cancer patients, each playing a role in mitochondrial dysfunction, increased autophagy, and apoptosis leading to protein degradation and muscle loss [14].

Cancer-related inflammation plays a significant role in the progression of solid tumors. The Neutrophil-to-Lymphocyte Ratio (NLR) is used as an indicator of systemic inflammation in cancer patients, where high NLR levels are associated with cachexia status in cancer patients. Cancer patients tend to experience cachexia, characterized by the reduction of both muscle and fat mass through complex processes. Chronic inflammation is often cited as one of the causes of this condition. Increased pro-inflammatory cytokines in the Tumor Microenvironment (TME) contribute to increased lipolysis activity, decreased lipase lipoprotein activity, and reduced lipogenesis in white adipose tissue, ultimately leading to decreased fat mass in cachexia conditions in NSCLC patients. [15,16]. However, different findings were observed in this study. Bivariate analysis results in this study revealed no association between NLR levels and the percentage of fat mass in NSCLC patients. This is consistent with previous studies [17]. This may be attributed to other mechanisms besides the inflammatory role that leads to the reduction of fat mass in cancer patients with cachexia. Firstly, there is a change in lipid metabolism by cancer cells as they grow and proliferate. Cancer cells require a large and rapid energy supply for proliferation and survival by altering cellular metabolism towards increased aerobic glycolysis. To meet this demand, adipose tissue releases triglycerides to be hydrolyzed into fatty acids. These free fatty acids are subsequently degraded and oxidized in cell mitochondria to be converted into ATP [18]. This is evidenced by the overexpression of mRNA Hormone Sensitive Lipase (HSL), which plays a role in the process of lipolysis in cancer patients with cachexia [10]. Additionally, cancer cells also produce a factor called Lipid Mobilizing Factor (LMF) that directly affects adipocytes to increase lipolysis. Secondly, the decrease in fat mass is caused by reduced food intake in NSCLC patients. Lipogenesis occurs when there is an excess of carbohydrate intake, which is then converted into triglycerides as fat reserves in adipose tissue. Side effects of the therapy such as nausea and vomiting lead to reduced intake in NSCLC patients.

In this study, a relationship between NLR levels and quality of life in NSCLC patients was found. NSCLC patients with high NLR levels were 3.563 times more likely to have poor quality of life compared to those with low NLR levels (p-value = 0.013; 95% CI 1.267-10.019). The multivariate analysis results showed that in the presence of high muscle mass and fat mass percentage, as NLR levels increased, the likelihood of having a good quality of life also increased (adjOR 0.217; 95% CI 0.054-0.875, p-value = 0.032). The differences in these results may be due to the interaction between the NLR variable and other variables such as fat mass and muscle mass, thereby affecting the outcome of the relationship between NLR levels and quality of life in NSCLC patients in this study. Secondly, the cut-off value for NLR for poor quality of life in NSCLC patients is still undetermined. The NLR cut-off value in this study was based on the NLR value in the study by Zhang et al. [19], which excluded patients with a history of steroid use in the last 6 months. While in this study, a history of steroid therapy was not excluded or controlled for in the analysis. The use of steroids can increase NLR levels. Steroids have a lympholytic effect on lymphoma cells, leading to lymphopenia. Additionally, steroids induce neutrophilia through several mechanisms such as increasing the release of neutrophils from the endothelial layer into the vascular stream, reducing neutrophil migration to extravascular sites, and increasing the rate of release of immature neutrophils from the bone marrow into circulation [20]. This may be the reason why the analytical test shows that high NLR levels are associated with a good quality of life. This was also found in the studies by Azuma et al. [21] and Lo et al. [20]. Until now, a precise cut-off value for NLR to assess the quality of life of NSCLC patients has not been established, thus further research on this matter is needed.

The group of patients with low muscle mass is at a 12.207 times higher risk of experiencing poor quality of life compared to NSCLC patients, with a 95% confidence interval ranging from 2.504 to 59.502 (p-value = 0.002) after controlling for confounding variables. A previous RCT study on 734 stage IIIB/IV NSCLC patients found that low muscle mass had a negative effect on physical function and role function (males; p-value = 0.016/0.020, females; p-value = 0.004/0.012), and global quality of life (p-value = 0.001) in males [22]. Systematic review and meta-analysis studies have also found an increased risk of death in lung cancer patients with muscle loss (HR 3.13; 95% CI: 2.06 – 4.76) and significantly shorter overall survival (p<0.001) [23]. Low muscle mass in advanced-stage NSCLC patients with cachexia is associated with poor quality of life. Progressive skeletal muscle atrophy in cancer cachexia leads to reduced energy and weakness (asthenia). This impacts physical activity and decreases the quality of life in cancer patients. Decreased skeletal muscle mass, which plays a role in balance, posture, and body movement, increases the risk of immobilization and prolonged bed rest in patients [24].

This will certainly affect the quality of life, especially in the patient's physical function domain and overall quality of life.

The selection of therapy for advanced-stage NSCLC patients primarily focuses on targeted therapy, chemotherapy, radiotherapy, and immunotherapy. Chemotherapy is one of the treatment options for advanced-stage NSCLC patients, especially for those who do not have genetic mutations. Administration of cytotoxic drugs can lead to side effects such as nausea, vomiting, and decreased appetite.

NSCLC patients with underfat body fat mass are at 9.128 times higher risk of having poor quality of life compared to NSCLC patients with normal-overfat body fat mass (95% CI: 1.417-58.805; p-value = 0.020) as determined by logistic regression analysis. Cancer patients undergo metabolic changes affecting body fat, including increased lipolysis activity, decreased lipoprotein lipase and lipogenesis activity, and increased thermogenesis. This leads to a decrease in body fat mass, resulting in weight loss in patients. NSCLC patients with high subcutaneous fat tissue volume have better Progression-Free Survival (PFS) ($p < 0.05$). The protective mechanism of subcutaneous fat tissue remains unclear, but there is a hypothesis suggesting that high subcutaneous fat content may prevent cancer cachexia and be associated with lower lipolysis processes [25].

A recent study from China with a sample of 750 NSCLC patients at all stages found that increased subcutaneous fat mass index (HR = 0.56, 95% CI 0.47–0.66, $p < 0.001$) and pericardial fat mass index (HR = 0.47, 95% CI 0.40–0.56, $p < 0.001$) were associated with longer overall survival [26]. Cancer patients require more energy, and fat is an important source of energy. Fat depletion occurs before muscle mass. Low-fat mass is also associated with poor treatment outcomes. A systematic review by Guo et al. [27] indicated that low-fat mass, whether subcutaneous, visceral, or both, is associated with worse progression-free survival (PFS) and overall survival (OS) in patients treated with immune checkpoint inhibitors (ICI).

This study has several strengths. First, to the best of the researchers' knowledge, this study is the first to investigate the relationship between muscle and fat mass with the quality of life of NSCLC patients in Bali. Second, the findings of this study can provide information and insights into factors influencing the quality of life of NSCLC patients in terms of patient nutrition, which can be used as a clinical reference for the comprehensive management of NSCLC patients.

This study has limitations. First, it collected data at a one-time point, thus unable to observe differences in the quality of life of patients at the time of initial diagnosis and after undergoing therapy. Second, it only addressed overall quality of life and did not discuss other functional domains.

## CONCLUSION

There is a relationship between NLR, muscle mass, and percentage of fat mass, with quality of life in non-small cell lung cancer (NSCLC) patients. There is a relationship between NLR and muscle mass in non-small cell lung cancer (NSCLC) patients. There is no relationship between NLR and percentage of fat mass in non-small cell lung cancer (NSCLC) patients.

## ACKNOWLEDGMENTS

All patients, all authors, and all support in paper

## DECLARATIONS

Funding: No funding sources Conflict of interest: None declared Ethical approval: The study was approved by Udayana University with the number 1882/UN14.2.2VII.14/LT/2023.

## 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: a cancer journal for clinicians. 2021;71(3):209-49.

[2] Barata F, Fidalgo P, Figueiredo S, Tonin FS, Duarte-Ramos F. Limitations and perceived delays for diagnosis and staging of lung cancer in Portugal: a nationwide survey analysis. Plos one. 2021;16(6):e0252529.

[3] Thronicke A, von Trott P, Kröz M, Grah C, Matthes B, Schad F. Health-Related quality of life in patients with lung cancer applying integrative oncology concepts in a certified cancer centre. Evidence-Based Complementary and Alternative Medicine. 2020;2020.

[4] 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(10).

[5] Fonseca GWPd, Farkas J, Dora E, von Haehling S, Lainscak M. Cancer cachexia and related metabolic dysfunction. International journal of molecular sciences. 2020;21(7):2321.

[6] Risnawati R, Pradjoko I, Wati F. Nutrisi pada Penderita Kanker Paru. Jurnal Respirasi. 2020;5(3):91.

[7] Aleixo GF, Shachar SS, Nyrop KA, Muss HB, Battaglini CL, Williams GR. Bioelectrical impedance analysis for the assessment of sarcopenia in patients with cancer: a systematic review. The oncologist. 2020;25(2):170-82.

[8] Cederholm T, Jensen G, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition–a consensus report from the global clinical nutrition community. Journal of cachexia, sarcopenia and muscle. 2019;10(1):207-17.

[9] Guo J, Chong FF, Yin LY, Lin X, Zhang MY, Shi ML, et al. Bioelectrical Impedance Phase Angle as a Predictors of mortality in patients with lung cancer: a prospective study. Journal of Nutritional Oncology. 2022;7(1):38-48.

[10] Weber BZC, Arabaci DH, Kir S. Metabolic reprogramming in adipose tissue during cancer cachexia. Frontiers in Oncology. 2022;12:848394.

[11] Ang L, Chan CPY, Yau W-P, Seow WJ. Association between family history of lung cancer and lung cancer risk: a systematic review and meta-analysis. Lung Cancer. 2020;148:129-37.

[12] Andarini S, Syahruddin E, Aditya N, Zaini J, Kurniawan FD, Ermayanti S, et al. Indonesian society of respirology (ISR) consensus statement on lung cancer screening and early detection in Indonesia. Jurnal Respirologi Indonesia. 2023;43(2):144-50.

[13] Baiu I, Titan AL, Martin LW, Wolf A, Backhus L. The role of gender in non-small cell lung cancer: a narrative review. Journal of thoracic disease. 2021;13(6):3816.

[14] Divella R, Gadaleta Caldarola G, Mazzocca A. Chronic inflammation in obesity and cancer cachexia. Journal of Clinical Medicine. 2022;11(8):2191.

[15] Yeom E, Yu K. Understanding the molecular basis of anorexia and tissue wasting in cancer cachexia. Experimental & Molecular Medicine. 2022;54(4):426-32.

[16] Siddiqui JA, Pothuraju R, Jain M, Batra SK, Nasser MW. Advances in cancer cachexia: Intersection between affected organs, mediators, and pharmacological interventions. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2020;1873(2):188359.

[17] Anissa L, Wulandari Y, Nurwidya F. Association Between Nutritional Status and Neutrophil Lymphocyte Ratio in Patients with Lung Cancer at Persahabatan Hospital, Indonesia. International Journal of Nutrition, Pharmacology, Neurological Diseases. 2021;11(3):199-205.

[18] Sreedhar A, Zhao Y. Dysregulated metabolic enzymes and metabolic reprogramming in cancer cells. Biomedical reports. 2018;8(1):3-10.

[19] Zhang Q, Song MM, Zhang X, Ding JS, Ruan GT, Zhang XW, et al. Association of systemic inflammation with survival in patients with cancer cachexia: results from a multicentre cohort study. Journal of Cachexia, Sarcopenia and Muscle. 2021;12(6):1466-76.

[20] Lo YT, Lim VY, Ng M, Tan YH, Chiang J, Chang EWY, et al. A prognostic model using post-steroid neutrophil-lymphocyte ratio predicts overall survival in primary central nervous system lymphoma. Cancers. 2022;14(7):1818.

[21] Azuma Y, Nakaya A, Fujita S, Satake A, Nakanishi T, Tsubokura Y, et al. Neutrophil-to-lymphocyte ratio (NLR) fails to predict outcome of diffuse large B cell lymphoma. Leukemia research reports. 2019;12:100173.

[22] Bye A, Sjøblom B, Wentzel-Larsen T, Grønberg BH, Baracos VE, Hjermstad MJ, et al. Muscle mass and association to quality of life in non-small cell lung cancer patients. Journal of cachexia, sarcopenia and muscle. 2017;8(5):759-67.

[23] Buentzel J, Heinz J, Bleckmann A, Bauer C, Roever C, Bohnenberger H, et al. Sarcopenia as prognostic factor in lung cancer patients: a systematic review and meta-analysis. Anticancer research. 2019;39(9):4603-12.

[24] Martin A, Freyssenet D. Phenotypic features of cancer cachexia-related loss of skeletal muscle mass and function: lessons from human and animal studies. Journal of cachexia, sarcopenia and muscle. 2021;12(2):252-73.

[25] Lee JW, Lee HS, Na JO, Lee SM. Effect of adipose tissue volume on prognosis in patients with non-small cell lung cancer. Clinical imaging. 2018;50:308-13.

[26] Tao J, Fang J, Chen L, Liang C, Chen B, Wang Z, et al. Increased adipose tissue is associated with improved overall survival, independent of skeletal muscle mass in non-small cell lung cancer. Journal of Cachexia, Sarcopenia and Muscle. 2023;14(6):2591-601.

[27] Guo H, Lin X-Y, Feng S, Wang C, Yuan L-Q, Sheng X-G, et al. Prognostic value of obesity in patients with cancer treated with immune checkpoint inhibitors: An updated meta-analysis and systematic review. Molecular and Clinical Oncology. 2024;20(1):1-15.