

Original Research Article

Relationship between anemia, hypoalbuminemia, vitamin D deficiency and quality of life in advanced non-small cell lung carcinoma patients at tertiary hospital in Bali

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ABSTRACT

Background: The main purpose of treatment in patients with advanced lung cancer is more emphasizing on prolonging survival and improving the patient's quality of life (QOL). Micronutrient deficiency has an impact on the patient's QOL. The purpose of this study was to analyse the relationship between biochemical parameters of nutrient deficiency with QOL in patients with advanced non-small cell carcinoma (NSCLC) at Sanglah hospital.

Methods: A cross sectional study was conducted in Sanglah general hospital on March-June 2021. Hemoglobin, albumin, and 2.5 (OH) D levels were obtained from patient's serum. The participant's QOL was measured with EQ-5D-3L questionnaire. Bivariate analysis using chi-square test or Fisher's exact test, and multivariate analysis using logistic regression.

Results: A total of 80 participants were included in this study, and 55% had poor QOL. Seventy percent participants had anemia, 36.3% had hypoalbuminemia, and 26.3% had vitamin D deficiency. The QOL of patients with advanced stage NSCLC was significantly associated with hypoalbuminemia ($p=0.000$) and vitamin D deficiency ($p=0.044$). Multivariate analysis showed that the most influential factor on the QOL of patients with advanced stage NSCLC was hypoalbuminemia (AOR 9.158; 95% CI 2.150-30.001; $p=0.003$).

Conclusions: Hypoalbuminemia and vitamin D deficiency were significantly related with QOL of advance NSCLC patients. No relationship was found between anemia and the QOL of advance NSCLC patients. Hypoalbuminemia was the most influential factors related to the QOL of advance NSCLC patients.

Keywords: Anemia, Hypoalbuminemia, Vitamin D deficiency, QOL, Advanced NSCLC

INTRODUCTION

Lung cancer is a malignancy that ranks first as a cause of morbidity in patients. NSCLC covers more than 80% of lung cancer cases. According to GLOBOCAN data, it is estimated that in 2018 the death rate from lung cancer was 1.8 million cases of death/about 18.4% of all cancer deaths.¹ Currently the treatment of lung cancer is growing rapidly, with more therapeutic options using individual approach. Despite significant improvements in treatment

efficacy and tolerability, survival was not significantly improved. Therefore, main goal in management of patients with advanced lung cancer is to maintain QOL as long as possible.²

Malnutrition, the course and stage of the disease, the severity of symptoms, and the impact of the therapeutic regimen significantly reduce the QOL of lung cancer patients.³ About 30-90% of lung cancer patients have an inadequate diet and nutritional intake. Lack of nutritional

intake, both macronutrients and micronutrients, has a detrimental effect on the immune system, tolerance to therapy, affects organ function and body metabolism. The effectiveness of treatment decreases, while side effects and complications of treatment increase. Mortality in cancer patients with impaired nutritional intake is about 30% higher.⁴ Biochemical examination in the blood is important for early detection of micronutrient deficiencies so that early intervention and therapy can be carried out in order to improve the QOL of lung cancer patients.

Anemia has a high incidence of around 74.4% in advanced stage NSCLC.⁵ Anemia causes fatigue, palpitations, sinus tachycardia, postural hypotension, vertigo, dyspnea, headaches, sleep disturbances, lethargy, and immunodepression.⁶ Hypoalbuminemia is also often found in advanced stage NSCLC which is about 81.8% of cases.⁷ Hypoalbuminemia can lead to extravascular fluid accumulation, increased risk of thromboembolic events, and decreased efficacy of albumin-bound drugs.⁸ Vitamin D deficiency leads to bone demineralization and impaired neuromuscular, thereby increasing the risk of falling and the incidence of pathological fractures.⁹ Vitamin D deficiency also causes a decreasing in patient's immune system, and as the result patient will be more susceptible to infection.¹⁰ The purpose of this study was to determine the relationship between anemia, hypoalbuminemia, and vitamin D deficiency with the QOL of patients with advanced NSCLC at Sanglah hospital.

METHODS

A cross sectional study was conducted in Sanglah general hospital, Denpasar, Bali started from March until June 2021. This study is an analytical observation research with cross-sectional design. The research participants were patients diagnosed with advanced stage NSCLC who underwent treatment at Sanglah hospital, and recruited by consecutive sampling.

Patient with NSCLC were diagnosed with lung cancer based on histopathology/cytology examination, and differentiated into squamous cell, adenocarcinoma, large cell, and other types of indistinguishable NSCLC. Advanced stage NSCLC is stage IIIB/IV based on international association for the study of lung cancer (IASLC) 8th edition TNM criteria. QOL is an individual's perception of his position in life according to the cultural context and value system in which they live and in relation to their goals, individual expectations, standards, and concerns. QOL was measured using the EQ-5D-3L instrument. QOL is said to be good if there are 3 dimensions worth 1. Anemia was defined as the haemoglobin level <12 g/dl in women and <14 g/dl in men according to National Cancer Institute (NCI), <12 g/dl in women and <14 g/dl in men. Hypoalbuminemia was defined as albumin serum level <3.5 g/dl. Vitamin D deficiency was determined as 25 (OH)D serum level <20 ng/ml.

Inclusion criteria were all patient diagnosed with advance NSCLC and underwent treatment in Sanglah general hospital, age more than 18 years old, and willing to participate in this study. Patients with malignancy other than NSCLC, patient with acute bleeding, under the diagnose of chronic kidney failure, nephrotic syndrome, or liver cirrhosis were excluded.

Patients with advanced stage NSCLC who came to the polyclinic or inpatient room at Sanglah hospital were interviewed and asked to fill out the EQ-5D questionnaire. Then venous blood was taken to measure the levels of haemoglobin, albumin, and vitamin D. Measurement of levels of 25 (OH) D using the chemiluminescence microparticle immuno assay (CMIA) method. Informed consent was obtained from all study participants. Ethics and licensing are completed according to the provisions. The collected data was then processed using IBM SPSS statistics 26.0. Bivariate analysis using chi-square test or Fisher's exact test, and multivariate analysis using logistic regression.

RESULTS

Eighty NSCLC participants met inclusion criteria, and 55% were female. Average age was 57.70 ± 9.86 years old, and the mean of body mass index (BMI) was 21.08 ± 3.59 kg/m². Only 25 participants (31.2%) had a history of smoking. Family history of cancer was found in 15 participants (18.8%). Adenocarcinoma was the most common histological type of NSCLC found in this study as many as 83.8%, and most of the participants (95%) were in stage IV. Metastatic pleural effusion was found in 60 participants (75%). Functional status of 73.7% patients scores 2 based on ECOG. A total of 34 participants (42.4%) didn't receive therapy, 22 participants (27.5%) underwent chemotherapy, 22 participants (27.5%) received targeted therapy, 1 subject (1.3%) underwent radiotherapy, 1 subject (1.3%) underwent combination therapy of radiotherapy and chemotherapy (Table 1).

Based on the EQ-5D-3L questionnaire, 44 people (55%) of the participants had poor QOL. QOL as assessed by the EQ VAS has a median value of 60, the highest score of 90 and the lowest score of 40 (Table 2). Most of the participants (86.2%) experienced problems in pain/ discomfort domain, some even experienced severe problems as much as 2.5% (Table 3). The mean of haemoglobin level in this study was 11.95 ± 1.84 g/dl. A total of 56 participants (70%) had anemia. The mean albumin level was 3.59 ± 0.57 g/dl and 36.3% of the participants had hypoalbuminemia. The mean serum 25 (OH) D level was 25.1 ± 8.74 ng/ml and 21 participants (26.3%) had vit D deficiency (Table 4).

Bivariate analysis showed 60.7% of anemic participants had poor QOL, but the relationship with QOL was not statistically significant (OR 2.164; 95% CI 0.818-5.723; $p=0.185$). Majority of participants with hypoalbuminemia (89.7%) have poor QOL. Difference in proportion of poor QOL in participants with hypoalbuminemia and with

normal albumin levels was 54.4%. It can be concluded that hypoalbuminemia had clinically and statistically significant relationship clinically and statistically with the participant's QOL. A total of 76.2% participants with 2.5 (OH) D levels below normal had poor QOL, and 52.5% participants with normal 2.5 (OH) D levels had a good QOL. Statistically, there was a significant relationship between vit D deficiency and the participants QOL (OR 3.543; 95% CI 1.148-10.932; $p=0.044$) (Table 5).

Multivariate analysis with logistic regression on the variables that in the bivariate analysis had a $p<0.25$, including gender ($p=0.095$), therapy ($p=0.008$), anemia ($p=0.185$), hypoalbuminemia ($p=0.000$), and vit D deficiency ($p=0.044$). Based on results of analysis showed that the most influential variable on the participants QOL was hypoalbuminemia with an adjusted OR of 9.158 (95% CI 2.150-39.001; $p=0.003$) (Table 6).

Table 1: Participant's characteristics, (n=80).

Characteristics	Mean \pm SD (range)	N	Percentage (%)
Gender			
Male		36	45
Female		44	55
Age (year)	57.70 \pm 9.86 (24-88)		
Body mass index (kg/m ²)	21.08 \pm 3.59 (13.84-32.45)		
Smoking history			
Non-smoker		55	68.8
Smoker		25	31.2
Family cancer history			
Yes		15	18.8
No		65	81.2
Histologic type			
Adenocarcinoma		67	83.8
Squamous		11	13.8
Other type		2	2.5
Disease staging			
III B		2	2.5
III C		2	2.5
IV A		41	51.2
IV B		35	43.8
Metastatic location			
Pleural effusion		60	75
Pericardial effusion		6	7.5
Contralateral lung		28	35
Bone		29	36.3
Liver		10	12.5
Brain		3 (3.8%)	3.8
Axilla		12	15
Thyroid		4	5
Performance status			
ECOG 1		21	26.3
ECOG 2		46	57.5
ECOG 3		13	16.2
Type of treatment			
Chemotherapy		22	27.5
Targeted therapy		22	27.5
Radiotherapy		1	1.3
Radiotherapy + chemotherapy		1	1.3
No treatment		34	42.4

Table 2: Overview of the participants QOL, (n=80).

Characteristics	Median (min-max)	N	Percentage (%)
Quality of life (EQ-5D)			
Good quality of life		36	45
Poor quality of life		44	55
EQ VAS	60 (40-90)		

EQ-5D: European quality of life-5 Dimensions; VAS: Visual analogue scale.

Table 3: Five dimensions in the EQ-5D, (n=80).

Variables	Mobility, n (%)	Self-care, n (%)	Usual activities, n (%)	Pain/discomfort, n (%)	Anxiety/depression n (%)
No problem	41 (51.2)	57 (71.3)	33 (41.3)	9 (11.3)	42 (52.5)
Some problem	29 (36.3)	5 (6.2)	25 (31.2)	69 (86.2)	38 (47.5)
Extreme problem	10 (12.5)	18 (22.5)	22 (27.5)	2 (2.5)	0 (0)
Total	80 (100)	80 (100)	80 (100)	80 (100)	80 (100)

Table 4: Participant's micronutrient levels.

Characteristics	Mean \pm SD (range)	N	Percentage (%)
Anemia			
No		24	30
Yes		56	70
Haemoglobin level (gr/dL)	11.95 \pm 1.84 (8-16.05)		
Hypoalbuminemia			
No		51	63.7
Yes		29	36.3
Albumin level (gr/dL)	3.59 \pm 0.57 (1.43-4.6)		
Vitamin D deficiency			
No		59	73.7
Yes		21	26.3
Vitamin D level (ng/ml)	25.1 \pm 8.74 (7.9-52.1)		

Table 5: Relationship between variables and QOL, (n=80).

Variables	Quality of life		OR, (95% CI)	P value
	Good, n (%)	Poor, n (%)		
Anemia				
No	14 (58.3)	10 (41.7)	2.164	0.185
Yes	22 (39.3)	34 (60.7)	(0.818-5.723)	
Hypo-albuminemia				
No	33 (64.7)	18 (35.3)	15.889	0.000
Yes	3 (10.3)	26 (89.7)	(4.219-59.832)	
Vitamin D deficiency				
No	31 (52.5)	28 (47.5)	3.543	0.044
Yes	5 (23.8)	16 (76.2)	(1.148-10.932)	
Gender				
Male	12 (33.3)	24 (66.7)	0.417	0.095
Female	24 (54.5)	20 (45.5)	(0.167-1.038)	
Age group (Years)				
<60	21 (46.7)	24 (53.3)	1.167	0.910
\geq 60	15 (42.9)	20 (57.1)	(0.479-2.839)	
Treatment				
Yes	27 (58.7)	19 (41.3)	3.947	0.008
No	9 (26.5)	25 (73.5)	(1.509-10.327)	

Table 6: The results of the logistic regression test of variables related to QOL.

Variables	Adjusted OR	95 % CI	P value
Anemia	1.756	0.519-5.940	0.365
Hypoalbuminemia	9.158	2.150-39.001	0.003
Vitamin D deficiency	3.163	0.854-11.709	0.085
Gender	0.808	0.259-2.518	0.713
Treatment	2.423	0.740-7.933	0.144

DISCUSSION

This study found more female participants, with a mean age of 57.70 ± 9.86 years, and adenocarcinoma was the most common histological type in the participants. According to data from the Respirasi nasional Persahabatan General Hospital in Jakarta, lung cancer is most commonly found in the 50-69 year age group.¹¹ Prior to 1990, the squamous type of NSCLC was the most common histologic type, especially in male patients. Over time the incidence of adenocarcinoma increases, especially in female patients. As a result, the proportion of adenocarcinoma is increasing in many countries in line with the increasing incidence of lung cancer in women.¹² Most of the metastases were found to be pleural effusion in 75% of the participants. This may be because most of the participants in this study had a histologic type of adenocarcinoma. Adenocarcinoma is more common in the lung peripheral and invades the pleura, so it is the most common histological type causing pleural effusion in patients (40%).¹³ Performance status (PS) of the participants in this study were mostly (73.7%) with ECOG scores 2 which indicates that the patient has decreased ability to perform daily activities. This is in accordance with research in Jakarta which showed the largest sample with an ECOG 2 score of 116 (50%) people.¹⁴ Participants who received therapy in the form of chemotherapy, targeted therapy, or radiotherapy had a higher QOL than who did not receive therapy. The therapy given can reduce some of the symptoms in patients such as pain and shortness of breath. With reduced symptoms, patients can perform their daily activities better and improve their QOL.²

Most participants within this study have a poor QOL. This finding matches with a research from Germany on 657 NSCLC participants, which found that the QOL of NSCLC patients was generally lower when compared according to age and sex in the general population (10 points, $p < 0.001$).¹⁵ Most of the research participants experienced problems with the dimensions of pain. A study by Polanski et al stated that pain is one of the complaints that most reduce the QOL of NSCLC patients, increasing the degree of pain lowers the score on the emotional dimension of the patient's QOL.³ Identification of the factors that affect the QOL, which are considered important by the patient is crucial. The multidimensional approach recommends symptom management in patients using pharmacological and non-pharmacological modalities.

Most of the participants in this study were suffered from anemia (70%). Similar results were also shown by research conducted at RSUP Dr Kariadi General Hospital in Semarang with prevalence anemia in patients with advanced stage NSCLC is 74.4%.⁵ The high incidence of anemia in lung cancer patients can be caused by malnutrition or malabsorption, inflammation chronic disease, metastatic infiltration of the bone marrow, and myelosuppression associated with therapy.¹⁶ A cohort

study in China with 140 patients advanced stage NSCLC undergoing chemotherapy found significant differences between patients with anemia and non-anemia in physical function scores, complaints, and QOL overall ($p < 0.005$). NSCLC patients with anemia have a lower QOL.¹⁷ Different results were obtained in this study, although most (60.7%) participants with anemia had poor QOL, but after the analysis, there was no statistically significant relationship between anemia and the patient's QOL. A case-control study in Spain on 355 patients using the EQ-5D-3L questionnaire also did not find a statistically significant difference on the QOL of lung cancer patients who suffer from anemia and those who do not have anemia (0.65 vs. 0.73, mean difference -0.18, $p = 0.6$). Relationship between anemia and QOL was not found due to low statistical power, and this problem can be solved by increasing sample recruitment in further studies.¹⁸ A randomized, double-blind, placebo-controlled trial of erythropoietin administration in patients with advanced stage NSCLC showed that despite the increased mean haemoglobin level was significant in the group receiving erythropoietin therapy for 12 weeks (20.6 g/L vs 2.1 g/L; $p = 0.003$), but there was no significant difference in improving the QOL scores of patients receiving received erythropoietin and placebo (6.5 vs 2.6; $p > 0.005$). This is because apart from the early termination of the study regarding the safety concerns of the study participants, the low proportion of patients who provided QOL data at week 12, made the trial not sufficiently powerful to find a significant difference in QOL.¹⁹ Anemia in cancer can be associated with a wide spectrum of symptoms, depending on the severity and speed of progression.¹⁶ Among the symptoms that arise due to anemia, fatigue is the most frequently reported complaint and subjectively is the deficit that most interferes with the QOL of NSCLC patients.²⁰ However, a study in Austria stated that the value of hemoglobin levels alone did not fully explain the fatigue felt by patients. In addition to Hb levels, several symptoms, especially pain, dyspnea, and sleep disturbances, also show an effect on fatigue.²¹

In this study only one third (36.3%) participants with hypoalbuminemia. Unlike previous researches in Persahabatan general hospital which found 81.8% NSCLC patients with hypoalbuminemia.⁷ Hypoalbuminemia condition in advance stage cancer is related to excessive energy expenditure caused by the increasing metabolism of tumor. In addition, there is also a decrease in albumin synthesis caused by reduced nutritional intake in patients.²² There was clinical and statistical significant relationship between hypoalbuminemia and the participant's QOL. In a study in Mexico, it was found that hypoalbuminemia was associated with loss of appetite (57.1 vs. 46.7; $p = 0.004$) and fatigue (58 vs. 46; $p = 0.01$). In addition, patients with hypoalbuminemia also show a tendency to experience nausea and neuropathy.²² Another study in Japan also suggested that hypoalbuminemia was associated with grade 3 non-hematological toxicity in elderly NSCLC patients undergoing chemotherapy.²³ Hypoalbuminemia was also associated with weight loss in

cancer patients (regression coefficient 2.2637; $p < 0.0001$). Weight loss from cancer is usually associated with decreased physical function mainly due to muscle wasting. Which later can lead to worsening of the patient's general condition and decreased performance status. Increased patient weight loss was also associated with decreased QOL (regression coefficient -0.0291; $p = 0.0002$).²⁴

A total of 26.3% of participants had vitamin D deficiency. A study in America from January 2008 to December 2010, of 359 patients who had just been diagnosed with an advanced stage NSCLC, 42.1% of participants had vitamin D deficiency. In this study also found patients with an ECOG score of 1-2 had less vitamin D deficiency than patients with an ECOG score of 3-4 ($p = 0.02$). In addition, patients who's still smoking have a greater prevalence of vitamin D deficiency compared with patients who had stopped smoking and patients who were not smokers ($p = 0.006$).²⁵ In another study in China the prevalence of vitamin D deficiency in patients with advanced stage NSCLC obtained as much as 75.9%. Vitamin D deficiency affects the patient's overall health, affecting neuro-skeletal responses, bone mineral density, insulin sensitivity, immune cell activity, cognitive function, and psychological health.²⁶ Decreased levels of vitamin D are also associated with a decrease in the patient's immune system because vitamin D is an immunomodulator that plays a role in the innate and adaptive immune systems.¹⁰ Vitamin D plays a role in inhibiting the development of cancer cells by triggering apoptosis and inhibiting angiogenesis.⁹ This study found a significant relationship between vitamin D deficiency and participant's QOL. A Canadian study found that a 100 nmol/L increase in serum 2.5 (OH) D levels increased HRQOL values by 29%. Adequate vitamin D levels are associated with functional status and mobility, as well as better mental health.²⁷ Other studies in Sweden involving cancer patients undergoing palliative care, after giving vitamin D supplementation for one month, there was a significant decrease in the dose of fentanyl compared to the untreated group with a difference of 46 g/hour; 95% CI 24-78. This dose difference increased after 3 months of vitamin D administration to 91 g/hour; 95% CI 56-140 g/hour. Measurement of QOL with the Edmonton symptom assessment scale (ESAS) score improved in the first month of vitamin D administration - 1.4; CI 95% -2.6-(-0.21). The vitamin D group also experienced a significant reduction in antibiotic use after 3 months with a difference of -26%; 95% CI -2.6-(-0.21). Vitamin D was also well tolerated 95 % CI by all patients and no side effects were reported.²⁸ In a study in Spain, vitamin D levels were found to be positively correlated with the disappearance of patient-reported fatigue complaints ($s = 0.49$), physical health ($s = 0.44$) and functional health ($s = 0.41$; $p < 0.01$).²⁹

From multi-variant analysis found that hypoalbuminemia was the most influential factor to QOL of advance NSCLC patient with adjusted OR 9.158. Hypoalbuminemia condition lowers the QOL for it leads to losing appetite, fatigue, edema, decreased drug efficacy, increases drug

toxicity, and increases the occurrence of thrombo-emboly on patient. Therefore, it is important for clinician to perform albumin level screening on advance NSCLC patient for earlier intervention. A study in China that involved advance NSCLC patient, albumin transfusion before chemotherapy proven to be effective to maintain albumin serum level during chemotherapy, even though patient has malnutrition or pleura effusion (36.5 ± 1.11 gr/L vs 35.22 ± 3.12 gr/L; $p > 0.05$). Albumin transfusion can also reduce the side effect of chemotherapy. Moreover, no systemic inflammation parameter escalation (NLR, PLR, dan CRP) was found in group which receives albumin transfusion.³⁰

Limitations of this research are confounding factors such as sunlight exposure, skin color, and nutritional consumption containing vitamin D, protein or iron that cannot be removed, and patient sample used for this study was only advance NSCLC. The advantage of this study is that the EQ-5D questionnaire is simple and easily understood by patients, and can provide clinicians with a quick and accurate picture of the patient's QOL. This study was the first research done in Bali so that it could used as the baseline study for further research.

CONCLUSION

In conclusion, most patients with advanced stage NSCLC had poor QOL. Hypoalbuminemia and vitamin D deficiency were significantly related with QOL of advance NSCLC patients. No relationship was found between anemia and the QOL of advance NSCLC patient. Hypoalbuminemia was the most influential factors related to the QOL of advance NSCLC patient. Efforts need to be made to improve the QOL of patients with stage NSCLC, one of them is supplementary therapy for micronutrient deficiency by giving albumin and vitamin D. Further research is needed to determine the relationship between micronutrient deficiency and the QOL of patients with advanced stage NSCLC at an early stage. In addition, it is also necessary to conduct further research with prospective methods to assess the relationship between anemia and QOL.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global Cancer Statistics 2018 : GLOBOCAN Estimates of Incidence and Mortality

- Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2018;68:394-424.
2. Milosevic B, Pejic D, Momcicevic D, Kovacevic P, Stanetic M, Dragic S. Quality of life in lung cancer patients due to treatment. *Signa Vitae.* 2016;11(2):47-50.
3. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. *Onco Target Ther.* 2016;9:1023-8.
4. Gröber U, Holzhauer P, Kisters K, Holick MF, Adamietz IA. Micronutrients in Oncological Intervention. *Nutrients.* 2016;8(163):1-30.
5. Supartono, Suryanto A. Faktor-faktor yang mempengaruhi ketahanan hidup satu tahun penderita kanker paru stadium lanjut di RSUP Dr. Kariadi Semarang. *Medica Hosp.* 2012;1(1):25-31.
6. Madeddu C, Gramignano G, Astara G, Demontis R, Sanna E, Atzeni V et al. Pathogenesis and Treatment Options of Cancer Related Anemia : Perspective for a Targeted Mechanism-Based Approach. *Front Physiol.* 2018;9:1-20.
7. Siregar YS, Widyaningsih W, Syahrudin E. Indeks Massa Tubuh , Persentase Otot Rangka dan Albumin pada Pasien Kanker Paru Karsinoma Bukan Sel Kecil Sebelum dan Setelah Kemoterapi Chemotherapy. *J Respir Indo.* 2016;36(2):73-82.
8. Rozga J, Piątek T, Małkowski P. Human albumin : old, new, and emerging applications. *Ann Transplant.* 2013;18:205-17.
9. Soejitno A, Kuswardhani RAT. Defisiensi vitamin D: mekanisme, implikasi, dan terapi pada lansia. *Cermin Dunia Kedokt.* 2009;36(2):81-3.
10. Foong RE, Zosky GR. Vitamin D Deficiency and the Lung : Disease Initiator. *Nutrients.* 2013;5:2880-900.
11. Jusuf A, Yahya WS, Hermansyah E. Epidemiologi Kanker Paru. In: Jusuf A, editor. *Dasar Dasar Diagnosis Kanker Paru.* 1st ed. Jakarta: Penerbit Universitas Indonesia; 2017;1-7.
12. Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. *Ann Glob Heal.* 2019;85(1):1-16.
13. Froudarakis ME. Pleural Effusion in Lung Cancer : More Questions than Answers. *Respiration.* 2012;83:367-76.
14. Ana F. Kesintasan Satu Tahun Penderita Karsinoma Paru Non-Small Cell Usia Lanjut Stadium IIIB/IV Yang Menjalani Kemoterapi Dibandingkan Dengan Non-Kemoterapi. 2014;1-129.
15. Hechtner M, Eichler M, Wehler B, Buhl R, Sebastian M, Stratmann J et al. Quality of Life in NSCLC Survivors-A Multicenter Cross-Sectional Study. *J Thorac Oncol.* 2018;14(3):420-35.
16. Busti F, Marchi G, Ugolini S, Castagna A, Girelli D. Anemia and Iron Deficiency in Cancer Patients : Role of Iron Replacement Therapy. *Pharmaceuticals.* 2018;1-14.
17. Xu C, Gao Y, Li L, Xing L, Liu S. Impact of Anemia on Chemotherapy Efficacy and Prognosis in Patients with Advanced Non-small Cell Lung Cancer. *Chin J Lung Cancer.* 2010;13(10):968-74.
18. Barca-hernando M, Muñoz-martin AJ, Rios-herranz E, Garcia-escobar I, Beato C, Font C et al. Case-Control Analysis of the Impact of Anemia on Quality of Life in Patients with Cancer : A Qca Study Analysis. *MDPI.* 2021;13(2517):1-11.
19. Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C et al. Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non-Small-Cell Lung Cancer With Disease-Related Anemia. *J Clin Oncol.* 2007;25(9):1027-32.
20. Carnio S, Stefano RF Di, Novello S. Fatigue in lung cancer patients : symptom burden and management of challenges. *Lung Cancer Targets Ther.* 2016;7:73-82.
21. Holzner B, Kemmler G, Greil R, Kopp M, Zeimet A, Raderer M et al. The impact of hemoglobin levels on fatigue and quality of life in cancer patients. *Ann Oncol.* 2002;13(6):965-73.
22. Arrieta O, Ortega RMM, Villanueva-rodríguez G, Serna-thomé MG, Flores-estrada D, Diaz-romero C et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer.* 2010;10(50):1-7.
23. Ikeda S, Yoshioka H, Ikee S, Morita M, Sone N, Niwa T et al. Serum albumin level as a potential marker for deciding chemotherapy or best supportive care in elderly , advanced non- small cell lung cancer patients with poor performance status. *BMC Cancer.* 2017;17(797):1-8.
24. Takayama K, Atagi S, Imamura F, Tanaka H, Minato K. Quality of life and survival survey of cancer cachexia in advanced non-small cell lung cancer patients-Japan nutrition and QOL survey in patients with advanced non-small cell lung cancer study. *Support Care Cancer.* 2016;24:3473-80.
25. Vashi PG, Edwin P, Popiel B, Gupta D. The relationship between circulating 25-hydroxyvitamin D and survival in newly diagnosed advanced non-small-cell lung cancer. *BMC Cancer.* 2015;15(1012):1-9.
26. Ma K, Xu W, Wang C, Li B, Su K, Li W. Vitamin D deficiency is associated with a poor prognosis in advanced non-small cell lung cancer patients treated with platinum-based first-line chemotherapy uncorrect proof version of versioncorre. *Cancer Biomarkers.* 2016;1:1-7.
27. Chao YS, Ekwaru JP, Ohinmaa A, Griener G, Veugelers PJ. Vitamin D and health-related quality of life in a community sample of older Canadians. *Qual Life Res.* 2014;23:2569-75.
28. Helde-Frankling M, Höijer J, Bergqvist J, Björkhem-Bergman L. Vitamin D supplementation to palliative cancer patients shows positive effects on pain and infections-Results from a matched case-control study. *PLoS One.* 2017;12(8):1-14.
29. Martínez-Alonso M, Dusso A, Ariza G, Nabal M. Vitamin D deficiency and its association with fatigue and quality of life in advanced cancer patients under

palliative care: A cross-sectional study. *Palliat Med.* 2016;30(1):89-96.

30. Wang X, Han H, Duan Q, Khan U, Hu Y, Yao X. Changes of serum albumin level and systemic inflammatory response in inoperable non-small cell lung cancer patients after chemotherapy. *J od Cancer Res Ther.* 2014;10(4):1019-23.

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