ORIGINAL ARTICLE

The Effect of Anemia on Prognostic in Non-Small Cell Lung Cancer Patients Receiving Platinum-Based Chemotherapy

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ABSTRACT

Introduction: Lung cancer has the highest incidence and mortality rate, which contributes to approximately 2.2 million cancer cases (11.4%) of total cancers worldwide. More than 70% of lung cancer cases present in the late, non-operable stage. Anemia is one of the conditions that could precipitate cancers and affect the patient's clinical presentation, including tissue oxygenation, organ function, and quality of life. It could also increase the risk of bleeding, post-operative mortality, and iron absorption rate in the case of ineffective erythropoiesis. All of these could affect the prognostic factor of the cancer. This study aimed to evaluate the effect of the severity of anemia on overall survival (OS) and progression-free survival (PFS) in non-small cell lung cancer (NSCLC) patients treated with platinum-based chemotherapy.
Methods: This was a retrospective cohort study involving 80 subjects of NSCLC patients treated with platinum-based chemotherapy from January 2018 to December 2020. Subjects were divided into two groups (39 patients in the normal group and 41 patients in the anemia group).
Results: The mean pre-treatment hemoglobin (Hb) was 10.55 ± 1.25 g/dL in NSCLC patients with anemia. The bone metastasis, OS, and PFS values of the normal and anemia groups were significant ($p = 0.008$; $p = 0.002$; $p = 0.27$). Anemia was significantly related to OS ($r = 0.146$, $p = 0.000$) and PFS ($r = 0.264$, $p = 0.000$) in NSCLC patients treated with platinum-based chemotherapy.
Conclusion: Higher severity of anemia can reduce OS and PFS in NSCLC patients treated with platinum-based chemotherapy.

INTRODUCTION

Based on the Global Cancer Observatory (GLOBOCAN) 2020 data, lung cancer accounts for 2.2 million cases (11.4%) of the total cancer incidence globally.[1] Lung cancer is the highest contributor to cancer incidence in men and the fifth largest contributor to cases in women in Indonesia.[2] At Dr. Saiful Anwar General Hospital, Malang, in 2017, non-small cell lung cancer (NSCLC) patients contributed 80-85% of all lung cancer cases, of whom >70% with non-operable, advanced stages required multimodality management methods such as radiotherapy, chemotherapy, or chemoradiation. Chemotherapy has been shown to prolong life with a 1-year survival rate of 15%.[3]

Anemia in malignancy is a condition that can aggravate the malignancy through direct tumor-associated such as inflammatory processes, blood loss, hemolysis, and invasion of malignant cells into the bone marrow or associated with chemotherapy or radiotherapy. Harrison, *et al*. (2000) conducted a retrospective review of data from 202 patients with cancer undergoing radiotherapy and found 45% of patients with anemia before radiotherapy had an increase to 57% after radiotherapy.[4] Anemia in cancer affects tissue oxygenation, organ function, quality of life, susceptibility to bleeding, postoperative mortality, and iron absorption. This condition impacts the prognostic factors of cancer as a whole. Therefore, overall survival (OS) and progression-free survival (PFS) data are required for NSCLC patients receiving platinum-based chemotherapy associated with the degree of anemia. This study was conducted to determine the effect of anemia degree on OS and PFS of NSCLC patients receiving platinum-based chemotherapy.

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METHODS

This was a retrospective cohort study based on data on the tumor status of NSCLC patients with the measured variables including PFS, OS, and degree of anemia before chemotherapy was given.

Clinical data

Samples were all secondary data on the tumor status of NSCLC patients whose diagnosis was confirmed by an anatomical pathologist who received platinum-based chemotherapy as the first-line therapy at Dr. Saiful Anwar General Hospital, Malang, from 1 January 2018 to 31 December 2020. The sampling method chosen was total sampling. All patients diagnosed with NSCLC via cytology and/or histopathology who had not received chemotherapy before except platinum-based one as first-line chemotherapy were included in this study. The exclusion criteria in this study were incomplete medical record data and patients with pulmonary metastasis from other organs. All patients who had hematological abnormality and chronic nephropathy as underlying diseases were also excluded from this study. The sample size taken in this study was 122 patients, but two patients were diagnosed with pulmonary tuberculosis, and six patients data obtained mutations after conventional chemotherapy. Therefore, it was continued with targeted therapy. Four patients continued chemotherapy outside Dr. Saiful Anwar General Hospital, Malang, one patient obtained a diagnosis of unknown origin, and 29 patients could not be contacted. Hence, they were excluded from the research subject. In the end, the total number of patient data sampled in this study was 80 patients.

Statistical treatment

Data were processed and analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) software version 24.0. OS data were analyzed using the Kruskal-Wallis test (abnormal distribution). Meanwhile, PFS data were analyzed using the one-way Analysis of Variance (ANOVA) test (normal distribution) to find the significant differences in OS and PFS values in each group of degree of anemia. The Mann-Whitney test was performed for abnormal distribution, and the Tamhane test for normal distribution. Pearson correlation test was used to test the correlation of anemia degree to OS and PFS.

RESULTS

The study was conducted at Dr. Saiful Anwar General Hospital, Malang, from June to July 2020. It obtained a sample of 80 people who met the inclusion and exclusion criteria. Forty-nine people had anemia, while 31 people did not have anemia.

Patient characteristics

As shown in Table 1, NSCLC was distributed the most in males (73.8%), smokers (90.0%), and people >40 years old (93.8%) with grade 1 anemia (47.5%). Adenocarcinoma was the most common (58.8%), with more patients without bone metastases (66.3%), and the most frequent therapy was platinum-based chemotherapy with a combination of carboplatin and paclitaxel (32.5%), followed by pemetrexed and carboplatin (30.0%). Conversely, OS and PFS each were the majority at <6 months. Survival year (OS) was found to be the most abundant, with 57 patients (71.3%) in less than 6 months. Meanwhile, the patients with PFS of <6 months were 77 patients (96.3%).

Relationship of anemia with clinicopathological parameters

Based on Table 2, the majority of patients with grade 1 anemia (47.5%) had an average hemoglobin (Hb) of 11.04 g/dL, but not much different from patients with grade 0 anemia or without anemia (normal), as much as 38.8% with an average Hb of 12.86 g/dL. The grade 3 anemia group had the lowest amount of 1.3%, with an average Hb of 6.90 g/L (12.5%). The initial Hb data were normally distributed. Hence, it was continued with the ANOVA test revealed that the average Hb between anemia degree 0, 1, 2, and 3 showed a significance value of 0.000 ($p < 0.05$). There was a significant difference in the average of Hb. Nevertheless, because there was only one case in the sample with grade 3 anemia, the results of the difference between groups in the post hoc test (pairwise comparisons between groups) could not be performed for initial Hb (gr/dL). Therefore, one case in grade 3 was included in grade 2 for further statistical purposes. Thus, it could be continued in the post hoc test, and the differences between groups of anemia degree were known.

Table 1. Demographic characteristics of study subjects (n=80)

Characteristics	N (%)
Age	
≤40 years old	5 (6.3)
>40 years old	75 (93.8)
Sex	
Male	59 (73.8)
Female	21 (26.3)
Smoking Status	
Non-smoker	8 (10.0)
Smoker	72 (90.0)
Anemia Grade	
Grade 0 (> 11.4 for male, >13.4 for female)	31 (38.8)
Grade 1 (<LLN – 10 gr/dL)	38 (47.5)
Grade 2 (<10 – 8 gr/dL)	10 (12.5)
Grade 3 (<8 gr/dL)	1 (1.2)
Histopatological Diagnosis	
Adenocarcinoma	47 (58.8)
Adenosquamous cell carcinoma	8 (10.0)
Squamous cell carcinoma	25 (31.3)
Bone Metastasis	
No	53 (66.3)
Yes	27 (33.8)
Chemotherapy Drugs	
Single-agent (gemcitabine/pemetrexed)	9 (11.3)
Paclitaxel + carboplatin	26 (32.5)
Pemetrexed + carboplatin	24 (30.0)
Gemcitabine + carboplatin	19 (23.8)
Vinorelbin + carboplatin	2 (2.5)
Survival Year (OS)	
<6 months	57 (71.3)
<1 year	16 (20.0)
<2 year	6 (7.5)
<3 year	1 (1.3)
Progression-Free Survival (PFS)	
<6 months	77 (96.3)
<1 year	3 (3.7)

Table 2. Initial Hb associated with anemia grade

Grade	Hb (mean ±SD, gr/dL)	N (%)	p
0	12.86 ± 1.34	31 (38.8)	0.000[a]
1	11.04 ± 0.79	38 (47.5)	
2	9.03 ± 0.82	10 (12.5)	
3	6.90 ± 1.71	1 (1.3)	

[a]With statistically significant difference from the ANOVA test

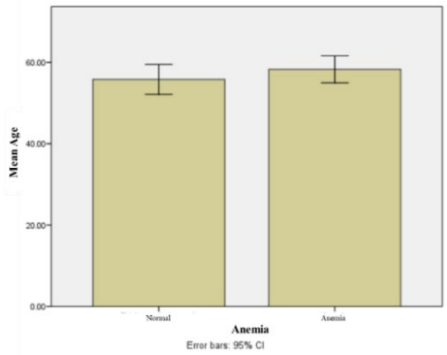


Figure 1. Graph of age comparison between normal and anemia group

Table 3 shows the analysis of the relationship between anemia and clinicopathological parameters. The number of patients belonging to the age group <40 years old and >40 years old between the group with anemia and the normal or non-anemic group was not significantly different ($p > 0.05$). Because the number of patients between the ages <40 years old and >40 years old in the two groups did not differ too much (Figure 1), the difference in frequency was not statistically significant. The same reason also made up why the comparison of sex, smoking status, histopathological diagnosis, and chemotherapy drugs with the anemia and normal group were all not statistically significantly different ($p > 0.05$). Meanwhile, there was a significant relationship between the variables of initial Hb, degree of anemia, metastasis to bone, OS, and PFS with anemia ($p < 0.05$).

The results indicate that the characteristics of age, sex, smoking status, histopathological diagnosis, and chemotherapy drugs in the anemic group and the normal or non-anemic group were still relatively homogeneous. Thus, confounding factors of age group characteristics, gender, smoking status, histopathological diagnosis, and chemotherapy drugs observed in both groups could be minimized not to affect the observed variables.

Clinicopathological univariate analysis with OS and PFS

There was no significant difference between the overall clinicopathological variables with OS and PFS ($p > 0.05$).

Table 3. Relationship of anemia with clinicopathological parameters

Clinicopathological Parameters	Normal, n=31 N (%)	Anemia, n=49 N (%)	p
Age			
Mean(±SD)[c]	55.81±9.99	58.28±11.46	0.326
≤40 years old[b]	1 (1.3)	4 (5.0)	0.377
>40 years old[b]	30 (37.5)	45 (56.8)	
Sex[b]			
Male	26 (32.5)	33 (41.3)	0.104
Female	5 (6.3)	16 (20.0)	
Smoking Status[b]			
Non-smoker	1 (1.3)	7 (8.8)	0.110
Smoker	30 (37.5)	42 (52.5)	
Initial Hemoglobin[c]			
Mean(±SD)	12.86±1.34	10.55±1.25	0.000*
Anemia Grade[b]			
Grade 0 (>11.4 for male, >13.4 for female)	31 (38.8)	0 (0.0)	0.000*
Grade 1 (<LLN-10 gr/dL)	0 (0.0)	38 (47.5)	
Grade 2 (<10-8 gr/dL)	0 (0.0)	10 (12.5)	
Grade 3 (<8 gr/dL)	0 (0.0)	1 (1.3)	
Histopatological Diagnosis[b]			
Adenocarcinoma	20 (25.0)	27 (33.8)	0.495
Adenosquamous cell carcinoma	2 (2.5)	6 (7.5)	
Squamous cell carcinoma	9 (11.3)	16 (20.0)	
Bone Metastasis[b]			
No	26 (32.5)	27 (33.8)	0.008*
Yes	5 (6.3)	22 (27.5)	
Chemotherapy Drugs[b]			
Single-agent	2 (2.5)	7 (8.8)	0.939
(gemcitabine/pemetrexed)	11 (13.8)	15 (18.8)	
Paclitaxel + carboplatin	11 (13.8)	13 (16.3)	
Pemetrexed + carboplatin	7 (8.8)	12 (15.0)	
Gemcitabine + carboplatin	0 (0.0)	2 (2.5)	
Vinorelbin + carboplatin			
Survival Year (OS)[b]			
<6 months	16 (20.0)	41 (51.3)	0.002*
<1 year	10 (12.5)	6 (7.5)	
<2 year	4 (5.0)	2 (2.5)	
<3 year	1 (1.3)	0 (0.0)	
Progression-Free Survival (PFS)[b]	28 (35.0)	49 (61.3)	0.027*
<6 months	3 (3.8)	0 (0.0)	
<1 year			

Note:
[b)] Mann-Whitney test; [c)] Unpaired t-test
[*)] If the $p < 0.05$ = significantly different/meaningful, and vice versa

Table 4 shows that the results of the comparison of age in the OS range, the number of patients with age categories, gender, smoking status, and anemia grade were almost the same as the significance value of the Chi-square test results, i.e., 0.443, 0.101, 0.938, 0.485, and 0.954 ($p > 0.05$), respectively. There were no significant differences in each comparison. Likewise, the results of the comparison of diagnoses based on histopathology, bone metastases, and chemotherapy drugs with the OS range showed a significance value of the Chi-square test results of 0.954, 0.538, and 0.546 sequentially ($p > 0.05$), which could mean that the OS ranges had a relatively similar number of patients in each clinicopathological parameters because they did not show any significant differences.

Table 5 shows no significant differences in all clinicopathological characteristics between the PFS group of less than 6 months and that of less than 1 year, where the number of patients belonging to the age of <40 years old and >40 years old between the group with PFS of less than 6 months and that with PFS of less than 1 year was not significantly different with a significance value of 0.649 ($p > 0.05$). The results of the sex comparison, smoking status, anemia grade, histopathological diagnosis, bone metastasis, and chemotherapy drugs had a relatively similar number of patients in the PFS category range with a significance value from the Chi-square test results of 0.292, 0.556, 0.177, 0.840, 0.988, and 0.967, respectively ($p > 0.05$).

Differences in the mean of initial Hb, OS, and PFS with degree of anemia

As depicted in Figure 2, the average values of the initial Hb of patients with anemia (degree 1 and 2) were 12.86 and 11.04 gr/dL, respectively, which were lower than the initial Hb of patients who did not have anemia (degree 0) with an average of 8.84 g/dL. A significant test result was obtained because of meaningful, significant differences in the initial Hb difference. The mean OS of patients with anemia (degree 1, 2, and 3 [mean OS 4.34 months, 2.8 months, and 1 month, respectively]) was lower than the OS of patients without anemia/normal (grade 0 with mean OS 8.03 months) (Figure 3). There was a significant difference in OS in the grade 0 anemia group with OS in the group with grade 1 and grade 2 anemia ($p < 0.05$). Meanwhile, the mean PFS of patients with anemia (degree 1 and 2) was lower (2.79 and 1.73 months) than the PFS of patients without anemia (grade 0), with a mean PFS of 4.64 months (Figure 4). There was a significant difference in PFS in the grade 0 group with anemia at grade 1 and grade 2 ($p < 0.05$). Likewise, PFS in the grade 1 group significantly differed from that in the group with grade 2 anemia ($p < 0.05$).

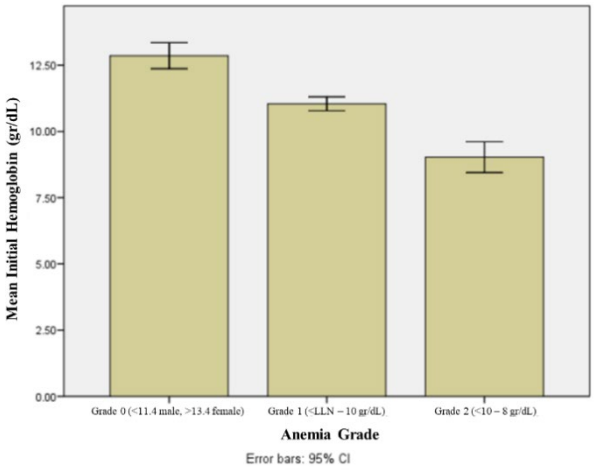


Figure 2. Comparison graph of mean initial Hb with anemia grade

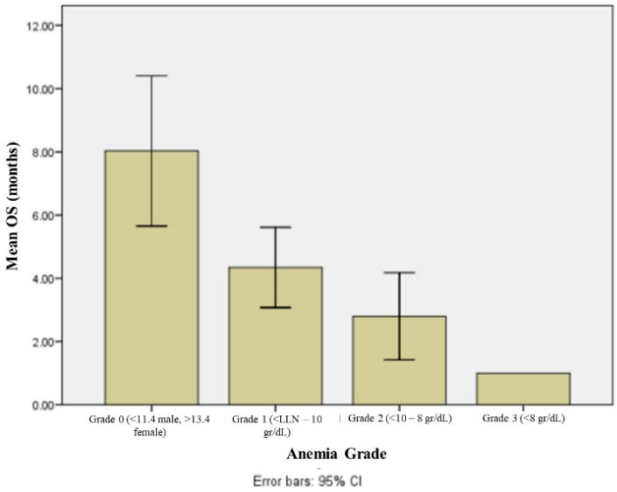


Figure 3. Comparison graph of mean OS by anemia grade

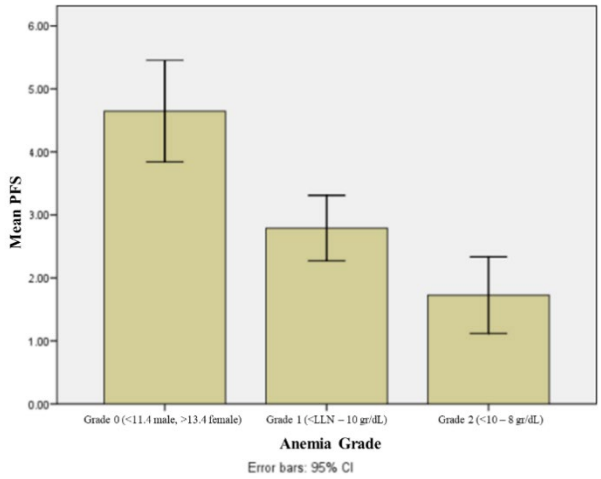


Figure 4. Comparison graph of PFS average by anemia grade

Table 4. Univariate analysis of clinicopathological parameters with OS

Clinicopathological Parameters	Overall Survival (OS)					p
	<6 months	<1 year	<2 years	<3 years	Chi-Square	
Age						
≤40 years old	3 (3.8)	2 (2.5)	0 (0.0)	0 (0.0)	1.628	0.443
>40 years old	54 (67.5)	14 (17.5)	7 (8.8)	0 (0.0)		
Sex						
Male	39 (48.8)	15 (18.8)	5 (6.3)	0 (0.0)	7.236	0.065
Female	18 (22.5)	1 (1.3)	1 (1.3)	1 (1.3)		
Smoking Status						
Non-smoker	6 (7.5)	1 (1.3)	1 (1.3)	0 (0.0)	0.675	0.879
Smoker	51 (63.8)	15 (18.8)	4 (5.0)	1 (1.3)		
Anemia Grade						
Grade 0 (>11.4 for male, >13.4 for female)	16 (20.0)	10 (12.5)	4 (5.0)	1 (1.3)	10.641	0.301
Grade 1 (<LLN-10 gr/dL)	31 (38.8)	5 (6.3)	2 (2.5)	0 (0.0)		
Grade 2 (<10-8 gr/dL)	9 (11.3)	1 (1.3)	0 (0.0)	0 (0.0)		
Grade 3 (<8 gr/dL)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Histopatological Diagnosis						
Adenocarcinoma	33 (41.3)	9 (11.3)	4 (5.0)	1 (1.3)	1.908	0.928
Adenosquamous cell carcinoma	6 (7.5)	1 (1.3)	1 (1.3)	0 (0.0)		
Squamous cell carcinoma	18 (27.5)	6 (7.5)	1 (1.3)	0 (0.0)		
Bone Metastasis						
No	35 (43.8)	12 (15.0)	4 (5.0)	1 (1.3)	2.439	0.486
Yes	22 (27.5	4 (5.0)	1 (1.3)	0 (0.0)		
Chemotherapy Drugs						
Single-agent (gemcitabine/pemetrexed)	8 (10.0)	1 (1.3)	0 (0.0)	0 (0.0)	10.800	0.546
Paclitaxel + carboplatin	19 (23.8)	7 (8.8)	0 (0.0)	0 (0.0)		
Pemetrexed + carboplatin	14 (17.5)	5 (6.3)	4 (5.0)	1 (1.3)		
Vinorelbin + carboplatin	14 (17.5)	3 (3.8)	2 (2.5)	0 (0.0)		
	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)		

Table 5. Univariate analysis of clinicopathological parameters with PFS

Clinicopathological Parameters	Progression-Free Survival (PFS)		Chi-Square	p
	<6 months	<1 year		
Age				
≤40 years old	5 (6.3)	0 (0.0)	0.208	0.649
>40 years old	72 (90.0)	3 (3.8)		
Sex				
Male	56 (70.0)	3 (3.8)	1.109	0.292
Female	21 (26.3)	0 (0.0)		
Smoking Status				
Non-smoker	8 (10.0)	0 (0.0)	0.346	0.556
Smoker	69 (86.3)	3 (3.8)		
Anemia Grade				
Grade 0 (>11.4 for male, >13.4 for female)	28 (35.0)	3 (3.8)	4.927	0.177
Grade 1 (<LLN-10 gr/dL)	38 (47.5)	0 (0.0)		
Grade 2 (<10-8 gr/dL)	10 (12.5)	0 (0.0)		
Grade 3 (<8 gr/dL)	1 (1.3)	0 (0.0)		
Histopatological Diagnosis				
Adenocarcinoma	45 (56.3)	2 (2.5)	0.349	0.840
Adenosquamous cell carcinoma	8 (10.0)	0 (0.0)		
Squamous cell carcinoma	24 (30.0)	1 (1.3)		
Bone Metastasis				
No	51 (63.8)	2 (2.5)	0.000	0.988
Yes	26 (32.5)	1 (1.3)		
Chemotherapy Drugs				
Single-agent (gemcitabine/pemetrexed)	9 (11.3)	0 (0.0)	0.561	0.967
Paclitaxel + carboplatin	25 (31.3)	1 (1.3)		
Pemetrexed + carboplatin	23 (28.8)	1 (1.3)		
Gemcitabine + carboplatin	18 (22.5)	1 (1.3)		
Vinorelbin + carboplatin	2 (0.5)	0 (0.0)		

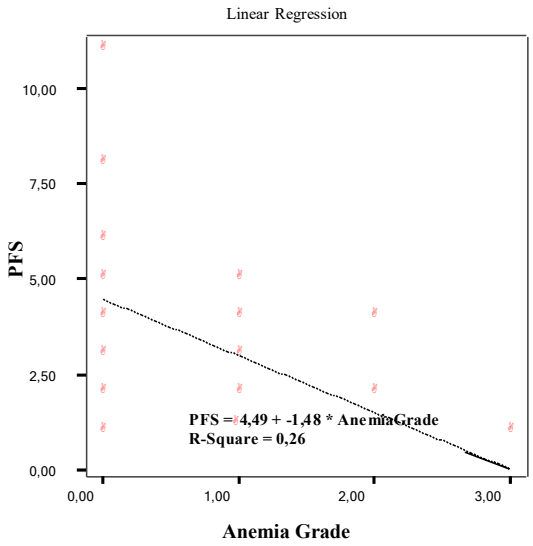
Effect of anemia on OS and PFS

There was a significant negative correlation between the degree of anemia and OS (r = -2.810; p = 0.000) and PFS (r = -1.485; p = 0.000) (Table 6). The higher the degree of anemia, the shorter the OS and PFS of NSCLC patients receiving platinum-based chemotherapy.

The regression test results for the effect of the degree of anemia on OS in NSCLC patients who were given platinum-based chemotherapy showed a p-value of 0.000. Therefore, the effect of the degree of anemia was significant in OS in NSCLC patients. The regression equation was Y = 7.68 - 2.810 X, where the constant number 7.68 means that if we do not consider the influence of the degree of anemia, the OS in NSCLC patients will remain constantly high. With a regression coefficient of -2.810 (negative value), it can be interpreted that the higher the degree of anemia, the significantly lower OS in NSCLC patients, and vice versa. The magnitude of the effect of the degree of anemia on OS in NSCLC patients showed an R-square value of 0.146, meaning that the effect of the degree of anemia on OS in NSCLC patients was 14.6%. In contrast, other factors influenced the other 85.4%. Moreover, the regression line between the degree of anemia and OS in NSCLC patients pointed to the lower right (Figure 5), which means that the higher the degree of anemia, the lower the OS in NSCLC patients, and vice versa.

The effect of the degree of anemia in PFS in NSCLC patients receiving platinum-based chemotherapy showed a p-value of 0.000. Hence, the effect of anemia was significant in PFS in NSCLC patients. The regression equation was Y = 4.495-1.485 X, where the constant number was 4.495. With a regression coefficient of -1.485 (negative value), it can be interpreted the same with OS, that the higher the degree of anemia, the significantly lower the PFS in NSCLC patients, and vice versa. The magnitude of the effect of the degree of anemia in PFS in NSCLC patients showed an R-square value of 0.264, meaning that the influence of the degree of anemia in PFS in NSCLC patients was 26.4%, whereas other factors influenced the other 73.6%. Based on the R-square value, it was known that the degree of anemia had the greatest influence on PFS in NSCLC compared to OS. The linear graph (Figure 6) shows that the regression line between the degree of anemia and PFS in NSCLC patients pointed to the lower right. This proves the linearity of the degree of anemia to PFS in NSCLC patients. This means that the higher the degree of anemia, the significantly lower the PFS in NSCLC patients, and vice versa.

The results of this test proved that the first hypothesis was correct, namely, the higher the degree of anemia, the shorter the PFS in NSCLC patients who were given platinum-based chemotherapy.



tabl 5. Linear graph of the effect of anemia grade in OS in NSCLC patients

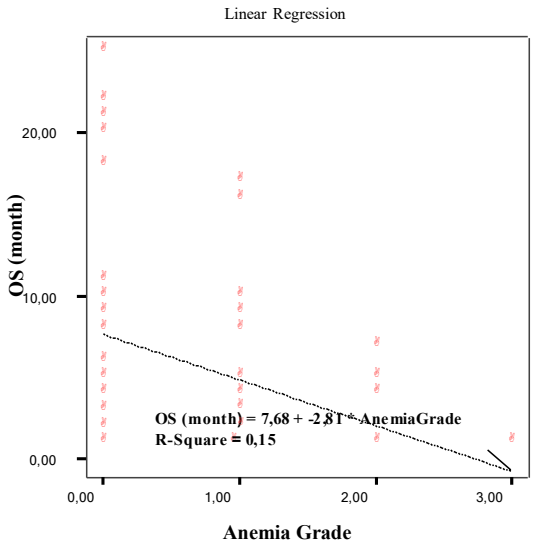


Figure 6. Linear graph of the effect of anemia grade in PFS in NSCLC patients

Table 6. The anemia grade affects test results in OS and PFS

Dependent Variables	Correlation Coef.	p	R-Square	Regression	p
Overall survival (OS)	-0.382	0.00	0.146	Y = 7.68-2.810 X where Y = OS, X = anemia grade	0.00
Progression-free survival (PFS)	-0.513	0.00	0.264	Y = 4.495-1.485 X where Y = PFS, X = anemia grade	0.00

DISCUSSION

The cases of lung cancer receiving platinum-based chemotherapy were found in patients aged <65 years old. Likewise, other studies concluded that NSCLC patients who received platinum-based chemotherapy showed that the mean of patients suffering from NSCLC was 58.9 years old.[4,5] Zhang, *et al*. (2020) stated that there was no significant difference in the age of patients with lung cancer in the study of inflammatory biomarkers at the beginning of therapy for adenocarcinoma-type NSCLC patients receiving platinum-based chemotherapy (p = 0.745).[6] Lung cancer was known to be found more common in men, with a percentage of 53.8-65.4%.[4,5,7]

The study results regarding smoking status were similar to studies conducted by Zhang, *et al*. (2020), Xie, *et al*. (2018), and Chen, *et al*. (2021), which stated that NSCLC patients receiving platinum-based conventional chemotherapy were found to be more common smoking patients (165 vs. 73 patients; 86 % vs. 14%; 59.4% vs. 40.6%).[6,8,9] The results of the anemia correlation with clinicopathological parameters in this study correlated similarly with other studies. Xiong, *et al*. (2017) stated that patient age did not correlate significantly with the incidence of anemia in NSCLC patients receiving platinum-based chemotherapy (p 0.539).[5]

Another study concluded that age had a significant relationship with risk factors for anemia (p = 0.008) by univariate analysis in NSCLC patients receiving platinum-based chemotherapy.[7] Kenar, *et al*. (2020) stated that characteristics of older age in patients when they were initially diagnosed with lung cancer had a 1.8 times higher risk of developing anemia (p = 0.04).[10] Gender was not associated with risk factors for anemia in NSCLC patients receiving platinum-based chemotherapy (p = 0.789).[7] By contrast, Zhang, *et al*. (2020) said gender correlated with the incidence of anemia in NSCLC patients receiving chemotherapy (p = 0.002).[6] In a study conducted by Han, *et al*. (2019), there was no significant difference between smoking status and the incidence of anemia (p = 0.49).[11] Of 82 patients with advanced lung cancer in Semarang, it was found that 61 patients (74.4%) had anemia when diagnosed with lung cancer.[12] A recent study showed 66.9% of patients with grade 0 anemia, 19.08% with grade 1 anemia, 10.8% with grade 2 anemia, 1.91% with grade 3 anemia, and 0.31% with grade 4 anemia.[9]

In Turkey, 74 patients with lung cancer aged over 65 years old showed no significant difference between the histopathological results of patients with lung cancer with anemia (p = 0.9).[13] Kenar, *et al*. (2020) stated that patients with cancer had a five times higher risk of developing anemia than the normal group of patients (p < 0.001) and had an even higher risk if accompanied by metastases (p = 0.008).[10] A study on 30 NSCLC patients with lung cancer who were given platinum-based chemotherapy in Persahabatan National Respiratory Referral Hospital, Jakarta, revealed that there was no significant difference between the hematological profiles of patients when they were initially diagnosed with platinum-based chemotherapy.[14]

In terms of the correlation between OS and clinicopathological parameters, Chen, *et al*. (2021) gave a conclusion that there was a significant difference between age characteristics where patients aged >60 years old had a shorter OS than those with NSCLC anemia who received platinum-based chemotherapy (p < 0.001).[9] Gender difference also had a significant relationship with the OS of NSCLC patients who were still operable (p = 0.001).[15] By contrast, Xu, *et al*. (2010) revealed that gender was not associated with OS in NSCLC patients receiving platinum-based chemotherapy (p = 0.364).[7] Zhang, *et al*. (2020) also stated that gender did not correlate with the duration of OS or PFS in NSCLC patients receiving chemotherapy (p = 0.313).[6] Additionally, this study suggested that there was no significant difference between smoking status with OS and PFS in patients with lung cancer (p > 0.05). Meanwhile, another study stated that smoking status was closely related to the OS of patients with stage IV NSCLC receiving chemotherapy with a significant value of p < 0.001.[9]

There was also a significant difference between the characteristics of the degree of anemia, histopathological diagnosis, and bone metastases in NSCLC patients receiving platinum-based chemotherapy with OS indicated by p < 0.001. However, for chemotherapy drugs received, there was no significant difference between the types of chemotherapy drugs received and the patients' OS (p = 0.865).[9] The group of patients with grade 0 or normal anemia had a higher OS of 28 months, which was followed by grade 2 and 3 anemia with OS of 17.5 months and grade 3 and 4 anemia with OS of 8.6 months. As Gascon, *et al*. (2019) mentioned, the group of patients with anemia, regardless of the degree, had a lower PFS of 4.27 months compared to the group of normal patients or without anemia with a PFS of 9.46 months.[16] Likewise, there was a trend of OS shortening in naive NSCLC patients with lung cancer with initial Hb levels below 12 g/dL.[9,17]

NSCLC patients with anemia had a shorter OS (17.4 months) versus those without anemia (28 months). Patients with grade 0 anemia or without anemia had an OS of 28 months, those with grade 1 and 2 anemia had an OS of 17.5 months, and those with grade 3 and 4

anemia had the shortest OS of 8.6 months.[9] Xu, *et al*. (2010) stated that patients with chronic kidney disease with anemia had a lower quality of life and chemotherapy efficacy, as well as a shorter life span.[7] Patients with normal pretreatment Hb levels (NPHb) have a greater chance of survival with a longer period, versus those with low pretreatment Hb levels (LPHb) (HR = 2.05; 95% CI, 1.63-2.57; p <0.001).[6] In a study conducted by Deng, *et al*. (2010), of 766 NSCLC patients who did not have anemia at the time of diagnosis, the OS was approximately 8.1 months versus 252 patients with anemia of approximately 6.3 months (p < 0.0001).[15] According to Lee, *et al*. (2017), of 135 patients with liquid-based cytology (LBC)-type lung cancer receiving platinum-based chemotherapy, 56 with anemia had an OS of approximately 9.8 months versus 78 patients without anemia at approximately 13.8 months (p < 0.045).[18] In another study, low Hb levels and a decrease in Hb levels can shorten OS and provide poor OS outcomes (HR 1.51, 95% CI 1.42-1.61).[19]

Anemia had been stated as a prognostic factor in patients with lung cancer at the first hospital visit, and survival was significantly shorter in 298 patients with anemia (Median Survival Time/MST: 7.5 months) than in 313 patients without anemia (MST: 11.8 months), p < 0.0001).[20] Liu, *et al*. (2019) concluded from 23 studies with a sample of 10,612 patients that patients with preoperative anemia had a 1.6-fold greater risk of death (HR = 1.58; 95% CI, 1.44 -1.75).[21] The changes in Hb levels of >2.6 times lower indicate shorter survival (HR = 1.40, 95%CI 1.31-1.5, p = 45x 10 -22).[22]

CONCLUSION

In conclusion, of the 80 NSCLC patients who received platinum-based chemotherapy, 49 patients experienced anemia, of which 47.5% had grade 1 anemia, 12.5% had grade 2 anemia, and 1.2% had grade 3 anemia. The higher the degree of anemia, the shorter the OS in NSCLC patients who were given platinum-based chemotherapy (p = 0.000).

Study Limitation

The limitation of this study was that this study only looked for the effect of anemia at diagnosis in OS and PFS without considering the history of transfusion or the degree of toxicity as first-line therapy in NSCLC patients receiving platinum-based chemotherapy.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Collecting data, drafting manuscript, concepting and designing the manuscript: UK, SDP, and TWA. Processing data analysis and discussion: UK, SDP, TWA and NS. All authors contributed and approved the final version of the manuscript.

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