Baseline anemia and anemia grade are independent prognostic factors for stage IV non-small cell lung cancer

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Abstract. The current study aimed to investigate baseline anemia in patients with stage IV non-small cell lung cancer (NSCLC) and its relationship with clinicopathological features and prognosis. The clinical data of 4,874 patients with stage IV NSCLC were analyzed. The incidence of baseline anemia was observed. The relationship between baseline anemia and clinicopathological features was analyzed. Kaplan-Meier method and multivariate COX regression model were used to analyze the relationship of baseline anemia and prognosis of patients with NSCLC. Anemia classification was based on the criteria established by the National Cancer Institute (NCI). The mean hemoglobin (Hb) was 123.32 ± 20.31 g/l in patients with stage IV NSCLC. The prevalence of baseline anemia was 32.09%, among which 19.08, 10.79, 1.91 and 0.31% had mild, moderate, severe, and life-threatening anemia, respectively. The prevalence of baseline anemia was higher in patients who were >60 years old, male, had smoking history, exhibited squamous cell carcinoma and bone metastasis, and the difference was statistically significant. Univariate analysis indicated that patients without anemia had longer overall survival (OS) compared with patients with baseline anemia (median OS: 28.0 months vs. 17.4 months, P<0.001). As the grade of anemia rises, it was indicated that OS became shorter. Patients with anemia grade 0 had the longest OS (median OS: 28.0 months), followed by patients with anemia grades 1 and 2 (median OS: 17.5 months). The patients with anemia grades 3 and 4 had the shortest OS (median OS: 8.6 months; P<0.001). Multivariate analysis demonstrated that baseline anemia and anemia grade were independent prognostic factors in patients with stage IV NSCLC. In conclusion, baseline anemia and anemia grade are independent prognostic factors in patients with stage IV NSCLC.

Introduction

Lung cancer has the highest morbidity and mortality in China (1); 80-85% of patients with lung cancer had non-small cell lung cancer (NSCLC), and the majority were advanced at the time of initial diagnosis. Tumor-associated anemia is one of the common concomitant diseases of malignant tumors (2). Tumor-associated anemia production can be caused by a variety of factors, including tumor factors or tumor treatment factors. Tumor-associated anemia is common in patients with lung cancer and is often dramatically increased due to cancer therapy, especially platinum chemotherapy (3-7). Tumor-associated anemia can cause a variety of clinical symptoms, seriously reduces the quality of life of patients, affects the patient's tolerance to treatment, and reduces tumor tissue sensitivity to treatment (8).

The relationship between tumor-associated anemia and lung cancer prognosis has been the focus of clinicians. A recent meta-analysis of 23 studies that included 10,612 patients showed that preoperative anemia was a prognostic factor of lung cancer (9), as compared with LC patients without anemia, those with pre-operative anemia were at a 1.6-fold greater risk of death (summarized HR=1.58; 95% CI, 1.44-1.75). Zhang YH (10) reported that patients with normal pre-treatment hemoglobin (NPHb) levels had a greater chance of surviving for longer period, than did patients with low pre-treatment hemoglobin (LPHb) levels (HR=2.05; 95% CI, 1.63-2.57; P<0.001); Mandrekar *et al* (11) reported that patients with low Hgb levels had significantly worse TTP and OS. Wan *et al* (12) report that compared to patients with a low Hb change ($|\Delta Hb|\leq2.6$), those having a $|\Delta Hb|>2.6$ exhibited a significantly shorter survival [hazard ratio=1.40, 95% confidence interval 1.31-1.50, P=$4.5x10(-22)$, Plog rank=$1.6x10(-39)$]. Aoe *et al* reported that anemia is a prognostic factor of patients with lung cancer at first hospital visit (13), survival was significantly shorter in 298 patients with anemia (median survival time (MST): 7.5 months) compared with 313 patients without anemia (MST: 11.8 months, P<0.0001). The majority of studies have shown that anemia is a prognostic factor of lung cancer, but controversy still exists; several studies have

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shown that anemia is not associated with the prognosis of lung cancer (14,15). In previous studies on the prognoses of anemia and lung cancer, anemia diagnostic criteria, and detection methods, the results may be biased due to the inconsistency of anemia research subjects. Therefore, in our single-center study, the baseline anemia of 4,874 patients with stage IV non-small cell lung cancer was used as the research object to minimize the interference of related factors.

This study retrospectively analyzed the incidence and grade of baseline anemia in 4,874 patients with stage IV non-small cell lung cancer in China. The relationship between baseline anemia and clinicopathological characteristics and their effects on prognosis were analyzed to further guide the treatment of lung cancer.

Materials and methods

Clinical data. Our study retrospectively analyzed anemia-related data in patients with stage IV NSCLC. A total of 4,874 patients who were admitted to the Zhejiang Cancer Hospital between January 2013 and June 2019 were eligible for the study. The inclusion criteria were as follows: i) Pathologically proven stage IV NSCLC tumor; ii) age >18 years old; and iii) have complete clinical data and follow-up information. The exclusion criteria were as follows: i) With hematological basic diseases; and ii) with chronic nephropathy. The follow-up period lasted until October 2019. Clinical staging was based on the 8th edition of Classification of TNM Lung Cancer (16). Subsequent treatments received by the patient includeradiotherapy, chemotherapy, targeted therapy and immunotherapy, some patients receive only one type of treatment, and some patients receive two or more therapies, combination therapy means that the patient receives two or more treatments. Targeted therapy is defined as targeted drugs corresponding to driver genes of lung cancer. Immunotherapy includes PD1/PD-L1 drug. The study was approved by the institutional review board of Zhejiang Cancer Hospital.

Grading of anemia. According to the anemia grading criteria established by National Cancer Institution (17), anemia is defined as having hemoglobin (Hb) levels of <120.0 g/l for males and <110.0 g/l for females. Anemia is further categorized into five grades based on the Hb level, as follows: Grade 0, normal Hb level; grade 1 (mild anemia), 100 g/l, normal level; grade 2 (moderate anemia), 80-100 g/l; grade 3 (severe anemia), 65-80 g/l; and grade 4 (life-threatening anemia), <65 g/l. Baseline anemia is defined as having hemoglobin levels of <120.0 g/l for males and <110.0 g/l for females at first visit to the hospital,and all patients did not receive radiotherapy, chemotherapy, targeted therapy or immunotherapy treatment.

Statistical treatment. The Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM Corp) was used to perform the statistical analysis. Quantitative variables were presented as means ± standard deviation (mean ± SD). The mean values from multiple comparisons were compared by using ANOVA followed by Bonferroni-Forsythe. The data was analyzed using χ^2. Survival analysis was conducted using the Kaplan-Meier method, and comparison was performed via log-rank test. Multivariate analysis was conducted using Cox proportional hazard regression model. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 4,874 eligible patients with stage IV NSCLC were included. Patients' sex, age, smoking history, tumor type, bone metastases, comorbidity, and treatment are summarized in Table I.

Prevalence of anemia. For the 4,874 patients who had record of Hb level, the prevalence of baseline anemia was 32.09%, with a mean Hb level of 123.32±20.31 g/l, of which 19.08% had mild anemia, 10.79% had moderate anemia, 1.91% had severe anemia, and 0.31% had life-threatening anemia (Table II).

Relationship between baseline anemia and clinical characteristics. Less female patients had baseline anemia than male patients (36.85 vs. 25.56%, P<0.001). Compared with younger patients, patients who are >60 years old had higher baseline anemia (34.41 vs. 29.31%, P<0.001). The prevalence of baseline anemia was highest in patients with squamous cell carcinoma (49.67%), followed by patients with other NSCLC types (36.93%). Adenocarcinoma had the lowest prevalence of baseline anemia (29.34%), P<0.001. Patients with smoking history had higher baseline anemia than nonsmokers (38.97 vs. 27.38%, P<0.001). Patients without bone metastases had less baseline anemia than those with bone metastases (34.38 vs. 30.11%, P=0.002). Prevalence of baseline anemia was slightly lower in patients with comorbidity than those without comorbidity (32.06 vs. 32.12%). However, the difference was not statistically significant (P=0.966) (Table III).

Univariate analysis of clinical features and prognosis. Univariate analysis shows the significant association of OS with sex, age, pathological type, bone metastasis, smoking history, chemotherapy, targeted therapy, immunotherapy, baseline anemia, and anemia grade. However, OS was not significantly associated with comorbidity and radiotherapy (Table IV). Patients without baseline anemia had longer OS than those with anemia (median OS: 28.0 vs. 17.4 months, P<0.001; Fig. 1). With rising grade of baseline anemia, OS became shorter. Patients with anemia grade 0 had the longest OS (median OS: 28.0 months), followed by patients with anemia grades 1 and 2 (median OS: 17.5 months). Patients with anemia grades 3 and 4 had the shortest OS (median OS: 8.6 months), P<0.001 (Fig. 2).

Multivariate analysis of clinical features and prognosis. Univariateanalysis of statistically significant sections, such as sex, age, pathological type, bone metastasis, smoking history, chemotherapy, targeted therapy, immunotherapy, baseline anemia, and anemia grade, were included in the COX multivariate regression model. Multivariate analysis showed that age, pathological type, bone metastasis, smoking history, targeted therapy, immunotherapy, baseline anemia, and anemia grade were independent prognostic factors of OS in patients with stage IV NSCLC (Table V).

Table I. Demographic characteristics of the study population (n=4,874).

Characteristic	N (%)
Sex	
Male	2,822 (57.90)
Female	2,052 (42.10)
Age (years)	
>60	2656 (54.49)
≤60	2218 (45.51)
Smoking history	
Yes	1,981 (40.64)
No	2,893 (59.36)
Tumor type	
Adenocarcinoma	3,872 (79.44)
Squamous cell carcinoma	455 (9.34)
Others NSCLC	547 (11.22)
Bone metastasis	
Yes	2,254 (46.25)
No	2,620 (53.75)
Comorbidity	
Yes	2,489 (51.07)
No	2,385 (48.93)
Radiotherapy	
Yes	1,627 (33.38)
No	3,247 (66.62)
Chemotherapy	
Yes	3,426 (70.29)
No	1,448 (29.71)
Targeted therapy	
Yes	2,830 (58.06)
No	2,044 (41.94)
Immunotherapy	
Yes	204 (4.19)
No	4,670 (95.81)
Combine therapy	
Yes	3,093 (63.46)
No	1,781 (36.54)

NSCLC, non-small cell lung cancer.

Table II. Frequency of first admission baseline cancer-related anemia in the current study.

Grade	Hb (mean ± SD, g/l)[a]	Number	Percentage
0	134.02±13.19	3,310	-
1	109.20±5.72	930	19.08
2	91.48±5.61	526	10.79
3	74.03±3.97	93	1.91
4	59.40±3.94	15	0.31
Total	123.32±20.31	4,874	32.09

[a]With significant statistical difference for pairwise comparisons between groups.

Discussion

Our study included 4,874 patients with stage IV NSCLC. This was the largest sample size of a research on anemia in NSCLC in China. The prevalence of baseline anemia was 32.09% with a mean Hb level of 123.32±20.31 g/l, of which 19.08% had mild anemia, 10.79% had moderate anemia, 1.91% had severe anemia, and 0.31% had life-threatening anemia. Most patients with baseline anemia showed mild to moderate anemia. The incidence of baseline anemia was slightly lower than that reported in other countries based on European populations (3) but slightly higher than that reported for American populations (6). ECAS is a prospective, observational, and epidemiological survey of the anemia in the European region. At ECAS enrollment, 37.6% of lung cancer patients had Hb levels of <12.0 g/dl (3). In a retrospective, observational study on anemia in patients undergoing chemotherapy for solid tumors in the United States, 7,001 patients with NSCLC were enrolled. At baseline, 16.1% of the patients were anemic with Hb levels of <11.0 g/dl, and 33.6% had Hb levels of <12 g/dl; the mean (SD) Hb at baseline was 12.7 (1.8) g/dl (6). The difference in results may be related to the different definitions of anemia. Therefore, a standardized and uniform anemia definition may lead to standardized diagnosis and treatment.

Aoe *et al* reported that in 611 cases of lung cancer in Japan, a significant correlation was found between anemia and age and Eastern Cooperative Oncology Group (ECOG) scores; however, anemia was not correlated with sex, histological type, clinical stage, or serum lactate dehydrogenase (13). The results of our study showed that female patients with baseline anemia were fewer than male patients with baseline anemia (36.85 vs. 25.56%, P<0.001). Compared with younger patients, patients who are >60 years old had higher prevalence of baseline anemia (34.41 vs. 29.31%, P<0.001). The prevalence of baseline anemia was highest in patients with squamous cell carcinoma (49.67%), followed by patients with other NSCLC types (36.93%). Patients with adenocarcinoma had the lowest prevalence of baseline anemia (29.34%), P<0.001. Our study shows that the proportion of non-smokers is relatively high compared with other study (18), which may be related to the population of the study. A data from the Asian population published by Zhang shows that the proportion of non-smokers is 42.8% (10), the proportion of non-smoking patients in our study is similar to Zhang's study. In addition, the proportion of female patients in our study is relatively high, while the proportion of female patients who smoke in China is very low; the proportion of patients receiving Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) targeted therapy in our study is higher, and the dominant population of EGFR-TKI targeted therapy is non-smokers. Patients with smoking history had higher baseline anemia than nonsmokers (38.97 vs. 27.38%, P<0.001). The results were consistent with those obtained in a retrospective study involving 416 NSCLC cases reported by Zhang *et al* in Henan, China (10). The study further confirmed the basic characteristics of anemia in

Table III. Relationship between baseline anemia and clinicopathological features in current study.

| Clinical features	Anemia-free group (n=3,310)	Anemia group (n=1,564)	χ^2	P-value
Sex			69.829	<0.001
Male	1782	1040		
Female	1528	524		
Age (years)			14.466	<0.001
>60	1742	914		
≤60	1568	650		
Smoking history			72.528	<0.001
Yes	1209	772		
No	2101	792		
Pathological type			83.857	<0.001
Adenocarcinoma	2736	1136		
Squamous cell carcinoma	229	226		
Others	345	202		
Bone metastasis			10.132	0.002
Yes	1479	775		
No	1831	789		
Comorbidity			0.002	0.966
Yes	1691	798		
No	1619	766		
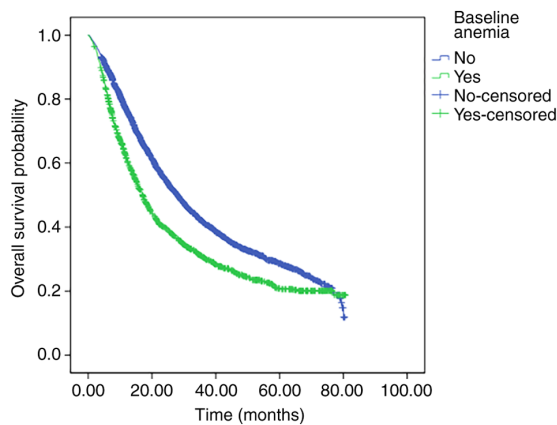
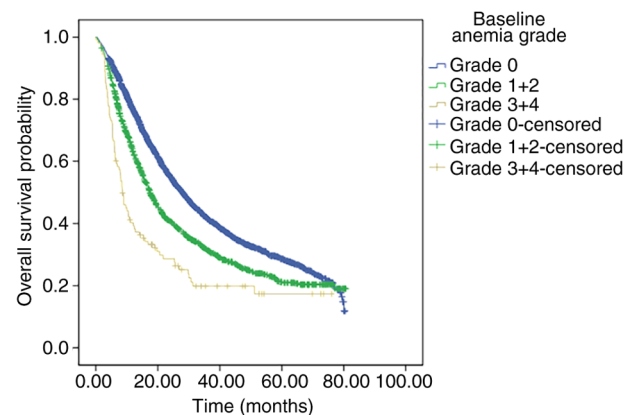Figure 1. Survival curve of patients with stage IV lung cancer with or without baseline anemia.

Figure 2. Survival curves of patients with stage IV lung cancer with different anemia grades.

Chinese lung cancer patients. The results of our study showed that patients without bone metastases had less baseline anemia than those with bone metastases (34.38 vs. 30.11%, P=0.002), considering that bone marrow invasion in patients with bone metastasis leads to a decrease in hematopoietic function.

According to previous studies on anemia and lung cancer prognosis, radiotherapy and chemotherapy are the main methods used to treat lung cancer (10,12,13,18,19). In the past decade, targeted therapy and immunotherapy have changed the treatment mode of advanced lung cancer. In our study, the proportions of patients undergoing chemotherapy, targeted therapy, radiotherapy and immunotherapy were 70.29, 58.06, 33.38 and 4.19%, respectively. The proportion of patients undergoing targeted therapy was higher, and immunotherapy

was included in the study; our research reflects the current treatment model for advanced lung cancer (20).

A meta analysis of 23 studies including 10,612 patients showed that preoperative anemia was a prognostic factor of lung cancer (9); patients with preoperative anemia had reduced OS after lung surgery. For patients with advanced lung cancer, the opportunity for surgery is lost; so, the result helps guide patients who will undergo surgery for treatment. Other studies also showed that anemia is associated with the prognosis of lung cancer, but the sample sizes are relatively small or they included multiple cancers (10-13). The evidence from studies investigating the relationship between anemia and the progression of NSCLC remains controversial, as several studies have shown that anemia is not associated with the prognosis of lung

Table IV. Univariate analysis of clinical features and prognosis in current study.

Clinical features	OS (months)	95% CI	χ^2	P-value
Sex			74.224	<0.001
Male	19.800	18.574-21.026		
Female	30.800	28.523-33.077		
Age (years)			52.673	<0.001
>60	20.400	19.198-21.602		
≤60	29.400	27.344-31.456		
Smoking history			90.913	<0.001
Yes	18.300	17.087-19.513		
No	29.200	27.296-31.104		
Pathological type			88.626	<0.001
Adenocarcinoma	26.900	25.575-28.225		
Squamous cell carcinoma	15.300	13.554-17.046		
Others	13.800	11.950-15.650		
Bone metastasis			32.394	<0.001
Yes	21.100	19.693-22.507		
No	27.100	25.323-28.877		
Comorbidity			0.729	0.393
Yes	22.800	21.067-24.533		
No	25.100	23.499-26.701		
Radiotherapy			2.030	0.154
Yes	25.200	23.030-27.370		
No	23.400	21.917-24.883		
Chemotherapy			8.371	0.004
Yes	23.100	21.758-24.442		
No	26.400	23.422-29.378		
Targeted therapy			182.633	<0.001
Yes	30.500	28.796-32.204		
No	15.700	14.629-16.771		
Immunotherapy			6.174	0.013
Yes	29.400	26.369-32.431		
No	23.800	22.599-25.001		
Anemia			84.801	<0.001
No (n=3,382)	28.000	26.480-29.520		
Yes (n=1,596)	17.400	15.887-18.313		
Grade of anemia			105.379	<0.001
0 (n=3,382)	28.000	26.480-29.520		
1+2 (n=1,146)	17.500	16.190-18.810		
3+4 (n=110)	8.600	6.857-10.343		

OS, overall survival; CI, confidence interval.

cancer (14,15). Our study is a single-center study with a large sample size that was performed in the real world in China. We analyzed the relationship between baseline anemia and prognosis in 4,874 patients with IV non-small cell lung cancer. Univariate analysis results showed that patients without baseline anemia had longer OS than those with anemia (median OS: 28.0 vs. 17.4 months, P<0.001). Further multivariate analysis revealed that baseline anemia was an independent prognostic factor in patients with stage IV NSCLC. Our conclusion is consistent with the relevant research results (9-13). The reason for the shortened survival of patients due to tumor-associated anemia is the decreased sensitivity to treatment and tolerance to treatment. According to the anemia grade, we divided the patients into three groups, namely, anemia grades 0, 1-2, and 3-4. With rising anemia grade, the OS became shorter. The patients with anemia grade 0 had the longest OS (median OS: 28.0 months), followed by patients with anemia grades 1 and 2 (median OS: 17.5 months). The patients with anemia grades 3

Table V. Multivariate analysis of clinical features and prognosis in current study.

Clinical features	B	SE	Wald	HR	95% CI	P-value
Sex	-0.068	0.053	1.655	0.934	0.842-1.036	0.198
Age	0.183	0.039	22.420	1.201	1.113-1.296	<0.001
Pathological type	0.151	0.028	28.567	1.163	1.100-1.229	<0.001
Bone metastasis	-0.261	0.038	47.710	0.770	0.715-0.829	<0.001
Smoking history	-0.160	0.052	9.481	0.852	0.7700-0.944	0.002
Targeted therapy	0.415	0.040	108.417	1.514	1.401-1.637	<0.001
Chemotherapy	-0.008	0.046	0.029	0.992	0.907-1.085	0.865
Immunotherapy	0.406	0.111	13.281	1.501	1.206-1.867	<0.001
Baseline anemia	-0.280	0.130	4.638	0.756	0.586-0.975	0.031
Grade of anemia	0.489	0.115	18.213	1.630	1.303-2.041	<0.001

SE, standard error; HR, hazard ratio; CI, confidence interval.

and 4 had the shortest OS (median OS: 8.6 months), $P<0.001$. Multivariate analysis showed that baseline anemia grade was also a prognostic factor of stage IV NSCLC patients. Results further confirmed the importance of baseline anemia for NSCLC, which requires attention and timely treatment (21). Treatment of tumor-associated anemia include the correction of nutritional deficiencies, use of intravenous (IV) iron, erythropoietic stimulating agents (ESAs), and blood transfusions (2), the use of ESAs is still controversial due to its security issues. The results of a phase III clinical study on ESAs treatment showed that Darbepoetinalfa dosed to a 12.0-g/dl Hb ceiling was noninferior to placebo for OS and PFS and significantly reduced odds of transfusion or Hb≤8.0 g/dl in anemic patients with NSCLC receiving myelosuppressive chemotherapy (21). The early treatment of anemia is very important. Whether management of anemia can improve the survival of patients, it may be an aim of future studies.

Our study had some limitations. The major limitation is its retrospective nature. Moreover, the study is a single-center study. However, as the largest sample size research on anemia in NSCLC, our results are meaningful and can serve as a guide for the treatment of NSCLC patients with anemia in China. In the future, multi-center prospective studies are needed.

The study showed that the prevalence of baseline anemia was highest in patients with stage IV NSCLC who are men, >60 years old, with smoking history, with squamous cell carcinoma, and with bone metastases. Baseline anemia and anemia grading were independent prognostic factors in patients with stage IV NSCLC.

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Availability of data and materials

Not applicable.

Authors' contributions

JZ designed the study. CC and ZS conceived of the study. CC and WW acquired the data. CC and ZS performed data analysis/interpretation. CC performed statistical analysis. CC prepared the manuscript. JZ revised the manuscript. The authenticity of all the raw data is confirmed by CC and JZ. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The current study was approved by the institutional review board of Zhejiang Cancer Hospital.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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