Pre-treatment hemoglobin levels are an independent prognostic factor in patients with non-small cell lung cancer

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Abstract. To date, few studies have reported the prognostic value of pre-treatment hemoglobin levels in patients with non-small cell lung cancer (NSCLC). In the present study, 416 patients with NSCLC were retrospectively reviewed. Univariate Cox proportional hazards regression analysis demonstrated 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). After adjustment for age, sex, tumor-node-metastasis stage, Karnofsky performance status, lung lobectomy, chemotherapy and radiotherapy, multivariate Cox proportional hazards regression analysis revealed that LPHb was an independent predictor for the poor prognosis of patients with NSCLC (HR, 1.86; 95% CI, 1.47-2.36; P<0.001). Estimation of the cumulative survival revealed that the overall survival of NPHb patients was significantly higher than that for LBHb patients (P<0.05), independent of whether the patients had received lung lobectomy or chemotherapy treatments. In conclusion, low pre-treatment hemoglobin levels were demonstrated to be an independent biomarker for poor prognosis in patients with NSCLC.

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Abbreviations: NSCLC, non-small cell lung cancer; TNM, tumor-node-metastasis; KPS, Karnofsky performance status; NPHb, normal pre-treatment hemoglobin; LPHb, low pre-treatment hemoglobin; HR, hazard ratio; CI, confidence interval; OS, overall survival

Key words: pre-treatment hemoglobin, non-small cell lung cancer, overall survival, case fatality rate, prognosis

Introduction

Lung cancer is a common cause of mortality for both men and women (1). Despite advances in treatment, the five-year overall survival (OS) rate is only 16.3% (2). In the majority of cases, >80% of lung cancer diagnoses are of the non-small cell lung cancer (NSCLC) type (3). To date, the disease prognosis is mainly based on the tumor-node-metastasis (TNM) staging system, the histologic type and certain mutational genetic analyses (3,4). Although these factors strongly affect the treatment choice and outcomes of patients with NSCLC, the majority of these factors cannot be determined without invasive procedures, and the required mutational genetics analysis procedures are costly and provide insufficient evidence for validation (5-7). Therefore, it is necessary and worthwhile to identify clinical biomarkers that could economically and conveniently predict the prognosis of patients with NSCLC.

Hemoglobin is a biochemical biomarker assessed during clinical examination. Several reports have indicated that low hemoglobin levels are associated with poor survival in patients with NSCLC (8-10); however, contradictory reports also exist (11,12). Whether hemoglobin levels, especially low pre-treatment hemoglobin (LPHb) levels, are an independent predictor for poor prognosis in patients with NSCLC requires further study for clarification.

In Henan, China, there reside ~1,000,000,000 people; to the best of our knowledge there is no regional data regarding the prognostic value of pre-treatment hemoglobin levels in patients with NSCLC. The aim of the present study was to investigate the prognostic value of pre-treatment hemoglobin levels for the survival of patients with NSCLC.

Patients and methods

Patients. From May 2010 to June 2017, 736 patients with lung cancer were diagnosed at the Henan University Huaihe Hospital (Henan, China). The clinical data were retrospectively collected. After excluding 320 ineligible subjects, a

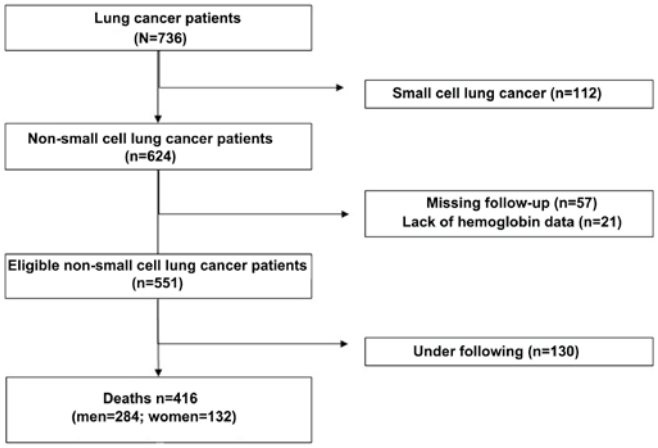

Figure 1. Schematic diagram of participant enrollment in the present study.

total of 416 patients with NSCLC (284 men and 132 women) were selected as subjects for the present study (Fig. 1). All cases of NSCLC were pathologically confirmed. The survival period for each subject was defined as the number of days from the date of diagnosis to the date of mortality. Patients were included in the present study if they had a verified diagnosis of NSCLC, regardless of whether they had received prior lung lobectomy, chemotherapy or radiotherapy treatments.

The clinical stage was assigned on the basis of the 8th Edition of the TNM Classification for Lung Cancer (13). Data regarding age, sex, histological cancer type, TNM stage, Karnofsky performance status (KPS) (14), lung lobectomy, chemotherapy, radiotherapy, smoking status, alcohol consumption, family history, diagnosis date, hemoglobin levels and date of mortality were obtained retrospectively from the patients' medical records, local death registration departments and telephone follow-ups. The study was approved by the Medical Ethics Committee of Henan University Huaihe Hospital.

Methods. The pre-treatment hemoglobin levels of the patients were obtained. The LPHb level was defined as <120 g/l of hemoglobin in men, and as <110 g/l in women. All patients were dichotomized into an LPHb group (n=104) and a normal pre-treatment hemoglobin (NPHb) group (n=312). Comparisons of clinical characteristics between the LPHb and NPHb groups were conducted using the Chi-squared (χ^2) test. For univariate Cox proportional hazards regression, age, sex, TNM stages, KPS scores, lung lobectomy status, chemotherapy, radiotherapy, smoking status, alcohol consumption, family history, and hemoglobin levels were dichotomized into a favorable group and an unfavorable group. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated to estimate associations between the observed factors and case fatality rate of patients with NSCLC. A subsequent multivariate analysis using Cox proportional hazards model estimated the prognostic influence of age, sex, TNM stage, KPS, lung lobectomy, chemotherapy, radiotherapy and hemoglobin levels on the case fatality rate of patients with NSCLC.

Survival curves were generated using the Kaplan-Meier analysis method, and the log-rank test was used to examine differences in survival between the various hemoglobin groups. All statistical analyses were performed using the Stata software version 13 (Stata Corporation, College Station, TX,

Table I. Pre-treatment hemoglobin levels among clinicopathological and lifestyle factors in NSCLC patients.

Factors	NPHb	LPHb	P-value
Age (years)			<0.001
≥65	140	64	
<65	172	40	
Sex			0.002
Male	200	84	
Female	112	20	
Histology			0.004
Adenocarcinoma	188	44	
SqCC	91	48	
Other	33	12	
TNM Stage			0.089
I-III	70	13	
IV	150	56	
Others	92	35	
KPS			0.005
<80	131	60	
≥80	181	44	
Lung lobectomy			0.006
Yes	79	13	
No	233	91	
Chemotherapy			0.020
Yes	148	63	
No	164	41	
Radiotherapy			0.066
Yes	57	11	
No	255	93	
Cigarette smoking			0.002
Yes	165	73	
No	147	31	
Alcohol drinking			0.112
Yes	61	28	
No	251	76	
Family history of cancer			0.994
Yes	18	6	
No	294	98	
Survival year			<0.001
<1 year	125	74	
≥1 year	187	30	

P-values were determined by Chi-squared (χ^2) test. NSCLC, non-small cell lung cancer; NPHb, normal pre-treatment hemoglobin (men, 120-160 g/l; women, 110-150 g/l); LPHb, low pre-treatment hemoglobin (men, <120 g/l; women ≤110 g/l); SqCC, squamous cell carcinoma; TNM, tumor-node-metastasis; KPS, Karnofsky performance status.

Table II. Univariate analysis of prognostic factors in patients with NSCLC.

Factors	Favorable	Unfavorable	Hazard ratio (HR)	95% CI	P-value
Age (years)	<65	≥65	1.19	0.98-1.45	0.078
Sex	Female	Male	0.90	0.73-1.11	0.313
TNM Stage	I-III	IV	1.55	1.28-1.89	<0.001
KPS scores	≥80	<80	1.50	1.24-1.83	<0.001
Lung lobectomy	Yes	No	1.96	1.55-2.48	<0.001
Chemotherapy	Yes	No	1.47	1.21-1.78	<0.001
Radiotherapy	Yes	No	1.34	1.03-1.74	0.030
Cigarette smoking	No	Yes	1.07	0.88-1.30	0.483
Alcohol consumption	No	Yes	0.95	0.75-1.20	0.660
Family history of cancer	No	Yes	0.93	0.62-1.39	0.720
Hemoglobin	NPHb	LPHb	2.05	1.63-2.57	<0.001

P-values were determined by univariate Cox proportional hazards regression analysis. NSCLC, non-small cell lung cancer; CI, confidence interval; TNM, tumor-node-metastasis; KPS, Karnofsky performance status; NPHb, normal pre-treatment hemoglobin (men, 120-160 g/l; women, 110-150 g/l); LPHb, low pre-treatment hemoglobin (men, <120 g/l; women ≤110 g/l).

USA). P<0.05 was considered statistically significant for all analyses.

Results

Patient characteristics. As presented in Table I, of the 416 patients, 178 (42.8%) were non-smokers and 238 (57.2%) were smokers. Histological diagnoses included 232 (55.8%) adenocarcinomas, 139 (33.4%) squamous cell carcinomas and 45 (10.8%) other NSCLC types. In total, 83 (20.0%) patients were at TNM stage I-III, 206 (49.5%) at stage IV and 127 (30.5%) patients had an unknown stage. Statistical analysis revealed that there were significant differences in hemoglobin levels between patients ≥65 and <65 years of age (P<0.001), men and women (P=0.002), histological types (P=0.004), KPS scores (P=0.005), treatment with or without lung lobectomy (P=0.006), treatment with or without chemotherapy (P=0.02), smokers and non-smokers (P=0.002), and survival time (P<0.001).

Univariate Cox proportional hazards regression analysis demonstrated that patients who were at TNM stage IV (HR, 1.55; 95% CI, 1.28-1.89), had KPS scores <80 (HR, 1.50; 95% CI, 1.24-1.83), did not receive lung lobectomy (HR, 1.96; 95% CI, 1.55-2.48), did not receive chemotherapy (HR, 1.47; 95% CI; 1.21-1.78), did not receive radiotherapy (HR, 1.34; 95% CI, 1.03-1.74), or had LPHb levels (HR, 2.05; 95% CI, 1.63-2.57) had a significantly increased case fatality rate (Table II). However, age, sex, smoking status, alcohol consumption and family history did not have any significant associations with the case fatality rate of patients with NSCLC (Table II).

Multivariate Cox proportional hazards regression analysis demonstrated that LPHb levels were independently associated with an increased case fatality rate (HR, 1.86; 95% CI, 1.47-2.36; Table III). In addition, not receiving lung lobectomy (HR, 1.46; 95% CI, 1.10-1.93), not receiving chemotherapy (HR, 1.34; 95% CI, 1.07-1.67) and TNM stage IV were also independent and unfavorable prognostic factors (Table III).

Kaplan-Meier survival curve estimations revealed that patients with LPHb had a poorer OS than did patients with NPHb levels (log-rank test, χ^2=39.50; P<0.001; Fig, 2A). When the patients were subdivided by sex, the male LPHb patients had a poorer OS than the male NPHb patients (log-rank test, χ^2=38.38; P<0.001; Fig. 2B), a difference not observed between the counterpart female groups (log-rank test, χ^2=3.16; P=0.076; Fig. 2B). When the patients were subdivided according to lung lobectomy, the LPHb group had a poorer OS than the NPHb group in both the no lung lobectomy group (log-rank test, χ^2=27.35; P<0.001; Fig. 2C) and the lung lobectomy group (log-rank test, χ^2=4.87; P=0.027; Fig. 2C). The subdivision of patients according to chemotherapy treatment also demonstrated that the LPHb group had a poorer OS than the NPHb group, in both the no chemotherapy group (log-rank test, χ^2=21.36; P<0.001; Fig. 2D) and the chemotherapy group (log-rank test, χ^2=12.30; P<0.001; Fig. 2D).

Discussion

The present data suggested that pre-treatment hemoglobin levels, measured at the time of diagnosis, may be an independent predictor for the prognosis of patients with NSCLC. These data are concordant with those of previous studies (8-10); to the best of our knowledge, this is the first report of associations between pre-treatment hemoglobin levels and the prognosis of patients with NSCLC, independent of whether they had received chemotherapy and/or lobectomy, in Henan, China. Compared with previous studies (8-11,15), the multivariate models performed in the current study included more factors, rendering the present results less confounded.

Low hemoglobin is common in oncological diseases, including in lung (16,17), breast (17), gastric (18) and ovarian cancer (19). There is evidence for a correlation between hemoglobin levels and the prognosis of patients with NSCLC. The precise underlying mechanisms are not fully understood. Tumor cells secrete a number of soluble molecules, including

Table III. Multivariate analysis of prognostic factors in patients with NSCLC.

Factors	Favorable	Unfavorable	Hazard ratio (HR)	95% CI	P-value
Age (years)	<65	≥65	1.01	0.82-1.25	0.892
Sex	Female	Male	0.90	0.72-1.12	0.356
TNM Stage	I-III	IV	1.31	1.04-1.65	0.022
KPS scores	<80	≥80	1.13	0.92-1.41	0.247
Lung lobectomy	Yes	No	1.46	1.10-1.93	0.008
Chemotherapy	Yes	No	1.34	1.07-1.67	0.011
Radiotherapy	Yes	No	1.09	0.82-1.45	0.558
Hemoglobin	NPHb	LPHb	1.86	1.47-2.36	<0.001

P-values were determined by multivariate Cox proportional hazards regression analysis. NSCLC, non-small cell lung cancer; CI, confidence interval; TNM, tumor-node-metastasis; KPS, Karnofsky performance status; NPHb, normal pre-treatment hemoglobin (men, 120-160 g/l; women, 110-150 g/l); LPHb, low pre-treatment hemoglobin (men, <120 g/l; women ≤110 g/l).

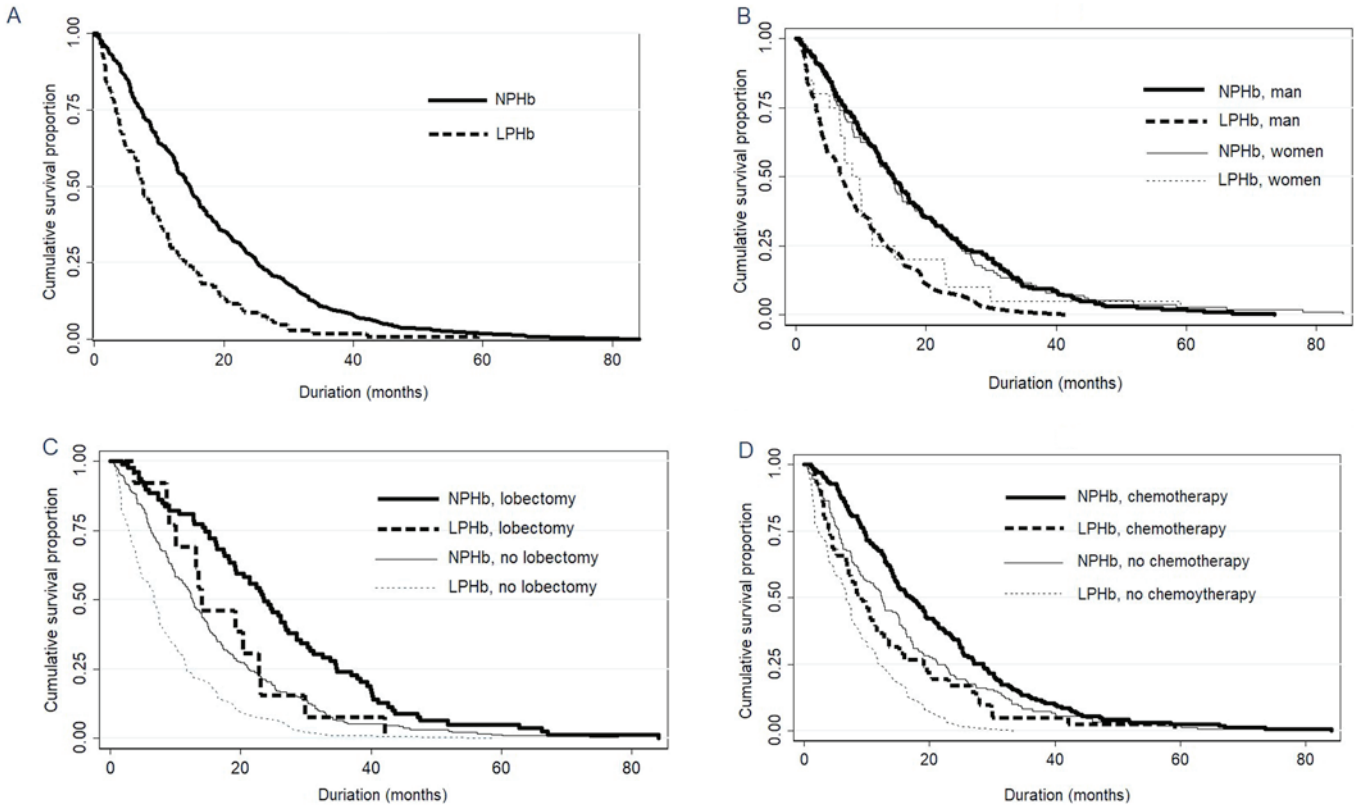

Figure 2. Cumulative survival proportion of patients with NSCLC according to their pre-treatment hemoglobin levels. (A) Overall survival of NPHb and LPHb patients with NSCLC (log-rank test, χ^2=39.50; P<0.001). (B) LPHb patients had a poorer overall survival than NPHb patients among men (log-rank test, χ^2=38.38; P<0.001), but not among women (log-rank test, χ^2=3.16; P=0.076). (C) LPHb patients had a poorer overall survival than NPHb patients in the no lung lobectomy group (log-rank test, χ^2=27.35; P<0.001) and the lung lobectomy group (log-rank test, χ^2=4.87; P=0.027). (D) LPHb group had a poorer overall survival than NPHb patients in the no chemotherapy group (log-rank test, χ^2=21.36; P<0.001) and the chemotherapy group (log-rank test, χ^2=12.30; P<0.001). NSCLC, non-small cell lung cancer; NPHb, normal pre-treatment hemoglobin (men, 120-160 g/l; women, 110-150 g/l); LPHb, low pre-treatment hemoglobin (men, <120 g/l; women ≤110 g/l).

interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). These molecules could decrease hemoglobin by changing the hematopoietic environment (20,21), suppressing erythropoiesis and erythropoietin (EPO) (22), and impairing the EPO response in erythroid progenitor cells (23). Furthermore, in patients with bone metastasis, bone marrow involvement may lead to bone morrow failure, which may then cause low hemoglobin levels (24) and subsequently lead to hypoxia, which could induce genomic changes and enhance the development of malignancy (25). Hypoxia may also boost tumor angiogenesis and accelerate metastasis (26). In addition, hypoxia may enhance tumor cell resistance to chemotherapy and radiotherapy through the development of multi-drug resistance (27).

A major strength of the present study was the inclusion of a large number of patients with NSCLC, all with a complete set of clinical data, including the pre-treatment hemoglobin levels, the complete survival period, records of multiple treatments, the family history and lifestyle details, including smoking status and alcohol consumption; this enabled us to investigate the prognostic value of pre-treatment hemoglobin levels with decreased sample bias and offset heterogeneity. However, there are also limitations to the present study. First, it was retrospective, and the information on post-treatment recurrence was insufficient. Second, these data did not observe interaction of post-treatment hemoglobin levels with survival rate.

Both lung lobectomy and chemotherapy treatments were associated with the prognosis of patients with NSCLC. However, neither significantly affected the prognostic value of the pre-treatment hemoglobin levels in the present study. The TNM stage was also independently associated with the NSCLC prognosis, which is in line with previous studies (28,29).

In conclusion, the present study suggests that low pre-treatment hemoglobin levels could be an independent biomarker for poor prognosis in patients with NSCLC. In future clinical studies, hemoglobin levels should be considered during the work-up of patients with NSCLC in prospective trials, in order to confirm its prognostic significance.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contirbutions

YHZ made substantial contributions to data collection and was a major contributor in writing the manuscript. YQL analyzed and interpretated the data, contributed to manuscript preparation and revision and gave final approval for the version to be published. HL was responsible for the acquisition of data and the Institutional Review Board application, conducted data interpretation, and gave final approval for the version to be published. MWZ and YMZ agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. XLL made substantial contributions to conception and design of the present study. PL and XYZ made substantial contributions to the design of the present study and acquisition of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Henan University Huaihe Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no compteing interests.

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