Impact of Preoperative Hemoglobin Level on Survival of Non-small Cell Lung Cancer Patients

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Abstract. *Background: Only a few studies have reported any prognostic impact of the preoperative hemoglobin level itself in resectable non-small cell lung cancer (NSCLC). The survival impact of preoperative hemoglobin level and the relationship between hemoglobin and serum CEA level were investigated. Patients and Methods: Two hundred and forty consecutive NSCLC patients were reviewed retrospectively. Results: The 5-year survival of patients with low and those with a normal hemoglobin level was 42.99% and 73.47%, respectively. Both univariate and multivariate analyses indicated the independent prognostic impact of the hemoglobin level. The result for stage I patients was identical. Patients with normal hemoglobin could be subdivided into 2 groups based on their serum CEA level; the 5-year survival of patients with normal and those with elevated CEA was 81.72% and 57.24%, respectively. Conclusion: The preoperative hemoglobin level was a prognostic factor for NSCLC patients. The combined use of hemoglobin and CEA levels might be useful to predict the prognosis of patients.*

Multiple prognostic factors have been reported in the literature for patients with NSCLC. However, the majority of these factors cannot be obtained preoperatively. Moreover some of these factors are available only as research tools.

Currently, serum carcinoembryonic antigen (CEA) level is the most inexpensive and routinely available preoperative factor measurable. Several reports have indicated that elevated preoperative serum CEA levels are associated with very poor survival after surgical resection (1-5). We believe that the measurement of such factors are important and should be valued. Among such preoperative factors, the hemoglobin level was reported as a prognostic factor (6-12). Although a low hemoglobin level was reported to impact outcome in patients with NSCLC receiving chemotherapy or radiation therapy (7-12), only a few studies have reported its impact on the outcome of patients with resectable NSCLC (13, 14). Moreover, its relationship with the CEA level is also unknown. In the present study, therefore, the prognostic impact of preoperative hemoglobin level and the relationship between hemoglobin and serum CEA in NSCLC were retrospectively investigated

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Patients and Methods

The present study was conducted from 2000 through 2004, including all patients with lung cancer who had a thoracotomy for intended surgical resection. Two hundred and forty consecutive lung cancer patients who underwent surgical resection were included in this study. There were 157 men and 83 women, with ages ranging from 26 to 85 years, with an average of 66.4 years. Overall follow-up periods ranged from 29 to 90 months.

The preoperative hemoglobin levels were obtained before invasive diagnostic procedures were performed. A low hemoglobin level was defined as a hemoglobin level <13.0 g/dl in men and 12.0 g/dl in women (7). The clinical investigation section of our hospital also measured preoperative serum CEA levels using the two-site immunoenzymometric assay; the normal upper limit for this assay was 5 ng/mL.

All patients underwent thoracotomy. Pathological (p) TNM staging was recorded in all patients. Follow-up information, including cause of death, was ascertained through a review of clinic notes and direct or family contact.

Comparisons of data between the two groups was made by using Fisher's extract test. Using linear regression analysis, the statistical correlation between preoperative hemoglobin and CEA level was assessed. Survival curves were obtained according to the Kaplan-Meier method. Comparison of survival curves was carried out using the log-rank test. Statistical calculations were conducted with JMP (SAS Institute Inc. Cary, NC, USA) and values of p less than 0.05 were accepted as significant.

Results

Eighty-eight patients (36.67%) were identified as having a low hemoglobin level at the time of their admission to our hospital. The frequency of a preoperative low hemoglobin level was 37.58% (59/157) in men and 34.94% (29/83) in women.

Table I. *Relationship between the preoperative hemoglobin level and clinicopathological factors.*

	Normal Hb	Low Hb	*P*-value
Age (years)			
≥65	90	55	0.616
<65	62	33	
Gender			
Male	98	59	0.686
Female	54	29	
Histology			
Adenocarcinoma	118	55	**0.039**
SqCC	23	21	
Other	11	12	
Stage			
I	105	56	0.387
II-IV	47	32	
CEA			
Normal	97	46	0.079
Elevated	55	42	

Hb: hemoglobin, SqCC: squamous cell carcinoma, CEA: carcinoembryonic antigen.

Table II. *Univariate analysis.*

Factor	Favorable	Unfavorable	Risk ratio	95% CI	*P*-value
Age	<65	≥65	1.0715	0.8620-1.2427	0.5379
Gender	Female	Male	1.5302	1.1929-2.0148	**0.0006**
Histology	Ad	Other	1.7325	1.3958-2.1451	**<0.0001**
pT	pT1	pT2-4	1.7826	1.4259-2.2570	**<0.0001**
pN	pN0	pN1-2	1.9860	1.5970-2.4619	**<0.0001**
CEA	Normal	Elevated	1.3174	1.0642-1.6314	**0.0116**
Hemoglobin	Normal	Low	1.5982	1.2911-1.9848	**<0.0001**

CI: confidence interval, Ad: adenocarcinoma, CEA: carcinoembryonic antigen.

Table III. *Multivariate analysis.*

Factor	Favorable	Unfavorable	Risk ratio	95% CI	*P*-value
Gender	Female	Male	1.2117	0.9170-1.6337	0.1806
Histology	Ad	Other	1.4096	1.1152-1.7785	**0.0043**
pT	pT1	pT2-4	1.3615	1.0683-1.7531	**0.0123**
pN	pN0	pN1-2	1.8028	1.4403-2.2503	**<0.0001**
CEA	Normal	Elevated	1.0720	0.8563-1.3415	0.5427
Hemoglobin	Normal	Low	1.4107	1.1290-1.7691	**0.0025**

CI: confidence interval, Ad: adenocarcinoma, CEA: carcinoembryonic antigen.

The relationship between the preoperative hemoglobin level and clinicopathological factors is shown in Table I. There was an association between hemoglobin level and histological type. The ratio of adenocarcinoma histology was smaller in patients having a low hemoglobin level. However, the hemoglobin level was not associated with gender, clinical stage or serum CEA level.

As shown in Figure 1A, the 5-year survival of patients with low and those with normal hemoglobin was 42.99% and 73.47%, respectively ($p<0.0001$).

The results of univariate analysis are summarized in Table II. The gender, histology, pT status, pN status, preoperative serum CEA level and preoperative hemoglobin level were related to patients' prognosis. The results of multivariate analysis including all variables for which $p<0.05$ on univariate analysis are summarized in Table III. Of the variables that were included in the multivariate analysis, histology, pT status, pN status and preoperative hemoglobin level were independent prognostic determinants.

In patients with stage I disease (n=161), as shown in Figure 1B, the 5-year survival of those with low and those with normal hemoglobin was 89.50% and 54.92%, respectively ($p<0.0001$). The 5-year survival of patients with a normal and those with an elevated serum CEA level was 68.95% and 50.98%, respectively ($p=0.00102$). Linear regression analysis revealed no significant relationship between the preoperative hemoglobin and serum CEA levels ($r^2=0.0004$, $p=0.7464$).

Patient groups by hemoglobin level were also subdivided based on the serum CEA level. As shown in Figure 2A, in patients with a normal hemoglobin level, the 5-year survival of those with normal and those with elevated CEA was 81.72% and 57.24%, respectively ($p=0.0097$). On the other hand, when patients had a low hemoglobin level (Figure 2B), both those with normal and those with elevated CEA had an unfavorable prognosis (40.27% *vs.* 44.55%; $p=0.8420$).

Discussion

A low hemoglobin level is the most frequently observed hematological abnormality faced by cancer patients (6). Yet, its impact on tumor biology is not well understood. Our results demonstrated that the hemoglobin level at the time of their admission is an independent prognostic factor. A low hemoglobin level was reported to impact outcome in NSCLC patients receiving chemotherapy or radiation therapy (7-12). However, these studies focused on patients with an advanced stage of the disease and only a few studies have reported its impact on the outcome of patients with resectable (early stage) NSCLC (13, 14). To avoid the effect of adjuvant therapies, we also examined the prognostic impact of low hemoglobin level in stage I patients. Our results also showed that a low hemoglobin level is a significant prognostic factor for stage I NSCLC

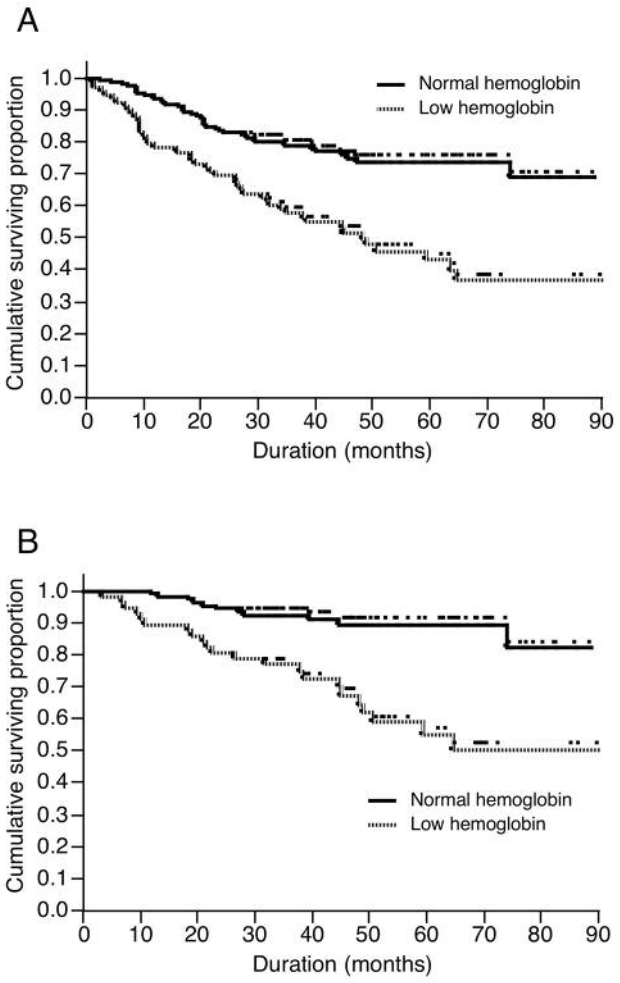

Figure 1. *Overall survival (A) and survival of stage I (B) patients according to their preoperative hemoglobin level.*

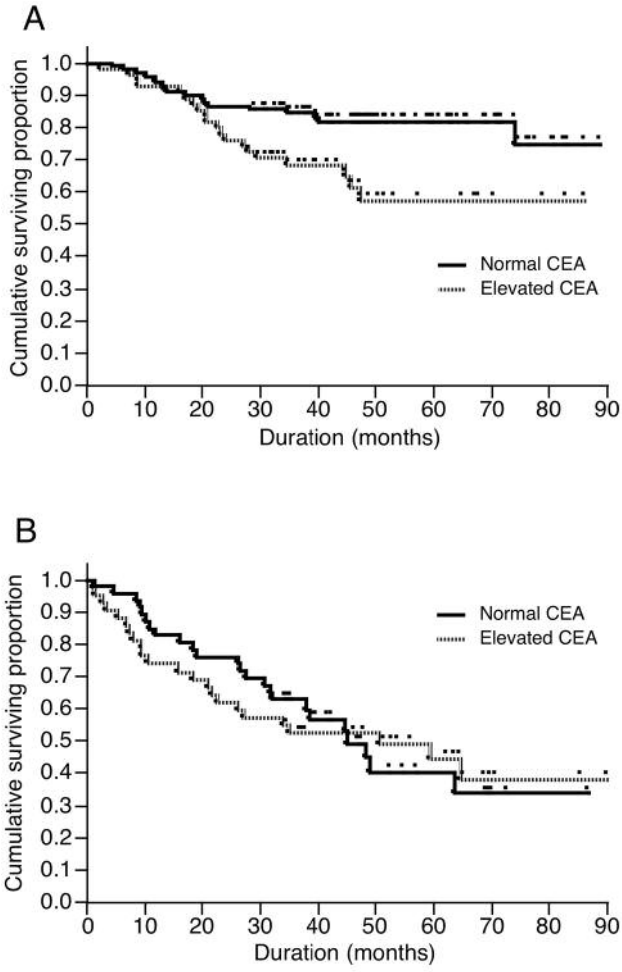

Figure 2. *Survival of patients with normal (A) and low (B) hemoglobin levels based on their preoperative serum CEA level.*

patients. However, it was impossible to determine whether a low hemoglobin level is the cause of poorer survival or a surrogate for other adverse factors.

Tumor cells are known to secrete soluble molecules. These molecules may cause hemolysis, suppression of erythropoiesis and impairment of erythropoietin response on erythroid progenitor cells. Moreover, in patients with bone marrow metastasis, a low hemoglobin level may be the result of bone marrow involvement. Accordingly, a low hemoglobin level may be regarded as a paraneoplastic phenomenon. Previous studies indicated that hypoxia can enhance malignant progression and may increase tumor aggressiveness through clonal selection and genomic changes (15, 16). Based on these findings, it is most likely that the strong association of the preoperative hemoglobin level with patients' survival is mainly due to a more aggressive tumor behavior.

Because of a lack of any relationship between the hemoglobin and CEA levels in our results, prognostic significances of hemoglobin and CEA levels might be due to different mechanisms. Thus we investigated the prognostic analysis by means of the combined use of hemoglobin and CEA levels. Our results showed that prognosis of patients with normal hemoglobin could be subdivided into two groups based on serum CEA level. Therefore, we believe that combined use of these is very useful to predict patients' prognosis. Currently, hemoglobin and CEA level are inexpensive and routine determinations. Despite current advanced diagnostic procedures for the preoperative staging, our results showed a role for preoperative hemoglobin level as an adjunct to conventional staging for NSCLC patients. Moreover, the combined use of hemoglobin and CEA levels might be useful to predict prognosis of patients.

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