RESEARCH ARTICLE

Pretreatment Serum Albumin Level is an Independent Prognostic Factor in Patients with Stage IIIB Non-Small Cell Lung Cancer: A Study of the Turkish Descriptive Oncological Researches Group

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Abstract

Background: Several prognostic factors have been studied in NSCLC, although it is unknown which is most useful. In this study, we aimed to investigate whether pre-treatment serum albumin level has prognostic value in patients with Stage IIIB NSCLC. Materials and Methods: This cross-sectional study included a total of 204 patients with Stage IIIB NSCLC who met the inclusion criteria. Pre-treatment serum albumin levels and demographic, clinical, and histological characteristics, as well as laboratory variables were recorded. A cut-off value was defined for serum albumin level and the patients were stratified into four groups on thios basis. Results: The majority of the patients was males and smokers, with a history of weight loss, and squamous histological type of lung cancer. The mean serum albumin level was 3.2±1.7 g/dL (range, 2.11-4.36 g/dL). A cut-off value 3.11 g/dL was set and among the patients with a lower level, 68% had adenocarcinoma and 82% were smokers. The patients with low serum albumin levels had a lower response rate to e first-line chemotherapy with a shorter progression-free survival and overall survival. Multivariate analysis showed that low serum albumin level was an independent poor prognostic factor for NSCLC. Conclusions: This study results suggest that low serum albumin level is an independent poor prognostic factor in patients with Stage IIIB NSCLC, associated with reduction in the response rate to first-line therapy and survival rates.

Keywords: Non-small cell lung cancer - serum albumin level - prognosis

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Introduction

Lung cancer, which is one of the most common cancers in men and women, is one of the leading causes of cancer-related deaths worldwide (Siegel et al., 2014). Non-small cell lung cancer (NSCLC) accounts for nearly 85% of all patients with lung cancer. About 80% of the patients have an advanced disease with a 5-year survival rate of 5 to 10% (Betticher et al., 2006; Siegel et al., 2014).

Several prognostic factors have been studied in NSCLC including stage, performance status, sex, age, and histological type, which are commonly used in the clinical practice (Berghmans et al., 2011). However, some authors have demonstrated that certain biological characteristics including lactate dehydrogenase, hypercalcemia, alkaline phosphatase, leukocytosis, and neutrophil counts, as well as patient characteristics including weight loss, smoking habits, comorbidities, and ethnicity and tumor features including histological degree, number of metastatic sites, vascular or local invasion, malign pleural effusion, and localization of the primary tumor may be potential prognostic factors in NSCLC.3-5 It is still unknown, however, which one is more useful and independent factor in the prognosis of the disease (Berghmans et al., 2011; Tanriverdi et al., 2014). Currently, certain molecular markers, genetic features, and treatment modalities have been suggested to be possible prognostic factors and have predictive values (Berghmans et al., 2008; Seculier et al., 2008). In recent years, a number of biomarkers having a prognostic impact have been widely studied in NSCLC (Tanriverdi et al., 2014).

Previous studies have shown that serum albumin

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level may have an adverse prognostic impact on certain cancer types and different cancer stages and that hypoalbuminemia is associated with poor prognosis (Gupta et al., 2009; Gupta and Lis, 2010; Ku et al., 2014; Zhang et al., 2014) In addition, the studies including patients with lung cancer have demonstrated that serum albumin level may play an important role in the scoring systems in metastatic patients (Espinosa et al., 1995; Maestu et al., 1997; Lai et al., 1998; Forrest et al., 2005; Win et al., 2008). The possible relationship between cancer and inflammation has been also widely studied in clinical trials (Lai et al., 1998). Serum albumin level, a critical inflammatory negative phase reactant, has been often investigated in the prognostic index models in patients with cancer. Similarly, certain inflammatory markers including C-reactive protein, distribution and rates of platelets, fibrinogen and blood cells have been co-studied with serum albumin level in scoring systems (Espinosa et al., 1995; Maestu et al., 1997; Lai et al., 1998). Some authors have also suggested that cancer cachexia is significantly associated with hypoalbuminemia (O'Gorman et al., 2000; McMillan et al., 2001). Although serum albumin level has been studied as a variable in scoring systems, there is no study investigating the impact of serum albumin level on the disease prognosis in a homogeneous patient population with Stage IIIB NSCLC in the literature.

In this study, we aimed investigate whether pre-treatment serum albumin level had a prognostic value in patients with Stage IIIB NSCLC.

Materials and Methods

In this cross-sectional study, medical records of a total of 674 patients with NSCLC with a confirmed histological diagnosis of primary lung cancer were analyzed between July 2006 and December 2014. Of these, 204 patients who met inclusion criteria with Stage IIIB NSCLC were included.

The time of diagnosis, age, sex, performance status, smoking status, weigh loss within the past three months, and histological type, degree, and size of the tumor were recorded. Laboratory variables included hemoglobin (Hb, g/dL), leukocycte count (10^^3/), neutrophil count (K/mL), platelet count (Plt, 10^3), serum lactate dehydrogenase (LDH, U/L), C-reactive protein (CRP, mg/L), and albumin (g/dL).

Exclusion criteria included diabetes mellitus, metabolic syndrome, hypertension, rheumatological diseases, hematological malignity, alcoholism, gut disease, neoadjuvant chemotherapy and/or radiation therapy, previous surgery for lung cancer, acute coronary syndrome and cerebrovascular disease within the past six months, local or systemic infection at the time of laboratory analysis, Stage I, II, IIIA, and IV disease, small-cell lung cancer, and missing data for the study variables.

The performance status was recorded according to the Eastern Cooperative Oncology Group (ECOG) performance status scores. All patients were staged according to the tumor-node-metastasis (TNM) criteria. The treatment response was assessed using the World Health Organization (WHO) criteria.

Blood samples were collected in an 8 to 12 hour fasting state. Lactate dehydrogenase was analyzed using the Abbott/Aeroset system™ (Abbott, Germany). Hemoglobin, leukocyte, neutrophil, and platelet counts were analyzed using the ABX-PENTRA 120 DX® Hematology Analyzer (ABX Diagnostics, France). C-reactive protein was measured using the turbidimetric method.

The protocol for this retrospective study was compatible with the local ethical guidelines and the Declaration of Helsinki. The study was approved by the academic and administrative committees in our centers.

The data are expressed in the mean±standard deviation or as the median and interquartile range (25 to 75%). The distribution of the variables was analyzed using the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, independent Student's t test. The Mann-Whitney U

Table 1. The Baseline Demograpical, Hictological, Clinical, and Laboratories Characteristics of All Patients in this Study

Characteristics	n (%) or level
Patients (n)	204
Age (years)	
<65	90 (44)
≥65	114 (56)
Gender (n, %)	
Male	147 (72)
Female	57 (28)
Smoking habits (n, %)	
Presence	161 (79)
Absence	43 (21)
Weight loss (>10 kg, in last 3 months) (n, %)	
Presence	106 (52)
Absence	98 (48)
ECOG performance status (n, %)	
0	47 (23)
1	120 (59)
2	37 (18)
Histological type (n, %)	
Adenocarcinoma	76 (37)
Squamous carcinoma	94 (46)
Adenosquamous carcinoma	9 (5)
Non-small cell lung cancer (not identified)	25 (12)
Tumor grade (n, %)	
Grade 1 (well differentiated)	16 (8)
Grade 2 (moderate differentiated)	104 (51)
Grade 3 (poor differentiated)	80 (39)
Unknown	4 (2)
First line chemotherapy regimen (n, %)	54 (27)
Cisplatin- docetaxel	32 (16)
Carboplatin- paklitaxel	91 (45)
Cisplatin- gemcitabin	27 (12)
Cisplatin-vinorelbine	
Baseline leukocyte count (x109)	10.3±4.6
Baseline neutrophils count (x109)	5.4±3.4
Baseline platelet count (x109)	368 ± 119
Baseline hemoglobin level (g/dl)	10.2±2.2
Baseline serum albumin level (g/dL)	3.4±1.7
Baseline CRP* level (mg/L)	24.6±14.8
Baseline serum LDH** level (U/L)	248±97

*C-reactive protein; **Lactate dehydrogenase

test was performed to assess non-parametric variables, while the Chi-square test and Fisher's test were used to assess qualitative parameters. Additionally, we used Spearman's test for correlation analyses. The Kruskall-Wallis test was used for the comparisons between clinical and demographic variables. In the univariate analysis, possible prognostic risk factor assessed using a model including age, sex, smoking habits, presence of weight loss, performance status, histological type, grading, 1st line treatment regimen, serum LDH, albumin, CRP, and Hb levels, count of leukocytes and platelets, and new metastatic sites. Than it was been tired because of assessment of independent risk factor by multiple logistic regression analysis. Moreover, Kaplan-Meier curve was used in survival analysis. A p value of <0.05 was considered statistically significant.

Results

A total of 204 patients with Stage IIIB NSCLC were included. The majority of the patients (72%) were men, 79% were smokers, 52% had weight loss more than 10 kg within the past three months, 51% had a modarate differentiated tumor, and 46% had an squamous carcinoma. Demographic, clinical, histopathological, and laboratory characteristics of the patients are shown in Table 1.

At the time for statistical analysis, 118 patients (58%) had died. The median follow-up was 34 months (range, 11 to 59 months).

Table 2. Comparison of Characteristics of Demographical, Histological, and Clinical and Analyses of Survival According to the Divided The Level of Serum Albumin

Characteristics	Group 1 (<2.11)	Group 2 (2.12-3.14)	Group 3 (3.15-4.01)	Group 4 (>4.02)	P*
Patients (n)	39	79	58	28	0.205
Age (n, %)					0.307
≤65 (years)	18 (46)	34 (43)	26 (45)	12 (43)	
≥65 (years)	21 (54)	45 (57)	32 (55)	16 (57)	
Gender (n, %)					0.48*
Male	27 (69)	68 (86)	41 (71)	11 (39)	
Female	12 (31)	11 (14)	17 (29)	17 (61)	
Smoking habits (n, %)					0.216
Presence	30 (77)	71 (90)	40 (69)	20 (71)	
Absence	9 (23)	8 (10)	18 (31)	8 (29)	
Weight loss (>10 kg, in last 3 months) (n, %)					0.117
Presence	19 (49)	41(52)	31 (53)	15 (54)	
Absence	20 (51)	38 (48)	27 (47)	13 (46)	
ECOG performance status (n, %)					0.038*
0	8 (21)	17 (22)	16 (28)	6 (21)	
1	24 (62)	49 (62)	30 (52)	17 (61)	
2	7 (17)	13 (16)	12 (20)	5 (18)	
Histological type (n, %)					0.191
Adenocarcinoma	15 (38)	22 (28)	25 (43)	14 (50)	
Squamous carcinoma	21 (54)	38 (48)	24 (41)	11 (39)	
Adenosquamous carcinoma	1 (3)	5 (6)	2 (4)	1 (4)	
Non-small cell lung cancer (not identified)	2 (5)	14 (18)	7 (12)	2 (7)	
Tumor grade (n, %)					0.107
Grade 1 (well differentiated)	3 (8)	7 (9)	4 (7)	2 (7)	
Grade 2 (moderate differentiated)	26 (67)	46 (58)	18 (31)	14 (50)	
Grade 3 (poor differentiated)	9 (23)	25 (32)	34 (59)	12 (43)	
Unknown	1 (2)	1 (1)	2 (3)	0	
Metastases sites after first-line chemotherapy (n, %)					0.037*
Liver	8 (21)	14 (18)	9 (15)	4 (13)	
Bone	5 (13)	8 (10)	5 (9)	1 (4)	
Adrenal gland	2 (4)	6 (7)	5 (9)	1 (4)	
Brain	14 (36)	7 (9)	1 (1)	1 (4)	
Multiple sites	10 (26)	44 (56)	38 (66)	21 (75)	
Baseline leukocyte count (x109)	10.4±3.7	9.3±3.5	8.7±3.1	8.1±2.4	0.028*
Baseline neutrophils count (x109)	5.4±3.1	5.3±1.7	3.8±2.4	3.7±1.9	0.041*
Baseline platelet count (x109)	401±108	394±89	314±74	311±49	0.031*
Baseline hemoglobin level (g/dl)	9.3±2.4	9.2±2.6	9.1±2.2	9.1±1.9	0.227
Baseline CRP level** (mg/L)	19.7±8.9	21.3±9.1	24.2±7.6	22.5±8.6	0.197
Baseline serum LDH*** level (U/L)	245±41	218±32	217±29	214±41	0.043*
Progression-free survival (months, median; 95% CI)	2 (95%CI 1.1-2.4)	3 (95%CI 1.4-3.1)	4 (95%CI 1.7-4.3)	4 (95%CI 1.9-4.6)	0.024*
Overall survival (months, median; 95% CI)	14 (95%CI 8.4-15.2)	22 (95%CI 9.4-23.7)	27 (95%CI 11.7-29.3)	31 (95%CI 19.4-35.2)	0.028*

*A two tailed p value of <0.05 was considered statistically significant **C-reactive protein; **Lactate dehydrogenase

The mean serum albumin level was 3.2±1.7 g/dL (range, 2.11 to 4.36 g/dL). The cut-off value was 3.11 g/dL. The patients were stratified according to the quartiles of serum albumin distribution with cut-off values ranging between <2.11 g/dL (the lowest quertile, Group 1), 2.12-3.14 g/dL (Group 2), 3.15-4.01 g/dL (Group 3) and >4.02 g/dL (the highest quertile, Group 4). Comparison of the groups in terms of study variables is shown in Table 2.

Among the patients with a serum albumin level of <3.11 g/dL, 68% had adenocarcinoma and 98% had smokers. The patients with low serum albumin levels had shorter progression-free survival (PFS) and overall survival (OS) rates. In addition, 39% of these patients had mostly brain metastasis. The patients with a serum albumin level of <2.11 g/dL had the shortest PFS and OS rates and the primary metastatic site was brain (Table 2).

There was a significantly positive correlation between low serum albumin level and the followings: adenocarcinoma histology (r=0.598, P=0.029), poorly differentiated tumor (r=0.618, P=0.024), smoking (r=0.621, P=0.031), female sex (r=0.496, P=0.042), increased serum CRP level (r=0.509, P=0.036), leukocytosis (r=0.645, P=0.028), and thrombocytosis (r=0.651, P=0.018).

The most common first-line treatment regimens were cisplatin-gemcitabine (n=91), cisplatin-docetaxel (n=54), carboplatin-paclitaxel (n=32), and cisplatin-vinorelbine (n=27). The median number of first-line chemotherapy cycles was 5 (range, 2 to 8). The overall response rate was 46% (including 34% partial response and 14% stable disease).

Following the first-line chemotherapy regimen, 42 patients were surgically treated and 54 patients underwent curative radiation therapy or chemo-radiation therapy. A total of 108 patients had progression following the first-line chemotherapy. Of these, 24 had a primary tumor or progression to the mediastinal lymph nodes, while 28 had lung metastasis or malign pleural effusion. Sixteen patients had also liver metastasis.

Table 3. Univariate and Multivariate Analysis of the Factors for Poor Survival in Non-Small Cell Lung Cancer with Stage IIIB

	Hazard ratios (95% CI)	P value
Univariate factors		
Age (<65 vs. >65 years)	1.42 (0.47-3.71)	0.274
Gender (male vs. female)	1.27 (0.94-2.58)	0.213
Smoking habits (presence vs. absence)	1.35 (1.03-2.45)	0.368
Weight loss (presence vs. absence)	1.89 (1.41-2.11)	0.198
ECOG performance status (0 vs. 1-2)	1.23 (1.04-3.47)	0.034*
Histological type (adenocarcinoma vs. squamous)	2.48 (1.18-3.94)	0.041*
Tumor grade (1 vs. 2-3)	1.41 (1.17-4.11)	0.037*
1st line chemotherapy regimen	1.96 (0.73-2.49)	0.287
Serum LDH level	1.75 (0.37-3.11)	0.241
Serum albumin level	3.11 (2.67-7.48)	0.018*
Baseline leukocyte count	2.04 (1.44-3.92)	0.034*
Baseline platelet count	1.47 (1.27-3.76)	0.041*
Baseline hemoglobin level	1.59 (0.49-2.17)	0.147
serum CRP level	1.98 (2.45-6.15)	0.037*
New metastatic site (brain vs. multiple sites)	1.77 (1.18-3.14)	0.034*
Multivariate factors		
Serum albumin level (<2.11 vs. >2.12)	3.11 (2.41-11.7)	0.021*

(* A two tailed p value of <0.05 was considered statistically significant); Abbreviations: CI, Confidence intervals; LDH, lactate dehydrogenase CRP, c-reactive protein

The median OS was 26 months (95% CI; 18.45-35.12) and median PFS was 8 months (95% CI; 4.52-7.18). The actual 1-, 2- and 5-year OS rates were 54.9%, 21.2%, and 6.4%, respectively. In patients with a serum albumin level of 3.11 g/dL, the median OS was 21 months (95% CI; 12.45-26.23) and the median PFS was 4 months (95% CI; 3.41-5.7), indicating a shorter survival rate, compared to the patients with a serum albumin level of >3.11 g/dL (P=0.024 and P=0.28, respectively). In addition, the patients with a serum albumin level of <3.11 g/dL had significantly reduced OS rates, compared to other patients (29% and 48%, respectively).

Univariate analysis showed that low serum albumin level, smoking, adenocarcinoma histology, increased serum CRP, increased platelet count, and hemoglobin level had a prognostic value (Table 3). In the multivariate analysis, low serum albumin level was found to be an independent prognostic factor for NSCLC (Table 3).

Discussion

In this study, we investigated whether pre-treatment serum albumin level had a prognostic value in patients with Stage IIIB NSCLC. The patients with a serum uric albumin level of <3.11 g/dL had lower response rate to the first-line chemotherapy with shorter PFS and OS rates. We found that low serum albumin level was an independent prognostic factor for NSCLC.

Serum albumin is the most simple and effective variable which shows visceral protein function. Therefore, it is commonly used in the assessment of malnutrition, inflammation, and hepatic dysfunction. Thus, malnutrition and inflammation are the major leading causes of suppression of the albumin synthesis. Normal serum albumin level ranges between 3.5 and 5.0 g/dL in adults. Hypoalbuminemia is defined as serum albumin <3.5 g/dL (Fearon et al., 1998; Margarson and Soni, 1998; Simons et al., 1999).

Several studies showed an inverse relationship between the body mass index and albumin synthesis, which is also an indicator of cancer cachexia (Fearon et al., 1998; Gupta and Lis, 2010). Gastrointestinal cancers and lung cancer are the most common cancer types presenting malnutrition and cancer-induced weight loss in all stages of the disease (Dewys et al., 1980; O'Gorman et al., 1998; von Meyenfeldt, 2005). However, serum albumin level may decrease due to inflammation in advanced cancer, cancer cachexia, malnutrition, chemotherapy-related malnutrition, prior surgery-related malnutrition, and terminal stage of the disease. Previous studies showed that hypoalbuminemia was an independent prognostic factor for gastrointestinal and lung cancers (Dewys et al., 1980; Margarson and Soni, 1998; O'Gorman et al., 1998; von Meyenfeldt, 2005).

In a study including 341 patients with NSCLC in 1997, Maestu et al. (1997) compared three prognostic scoring systems (Royal Marsden Model, London Group Scoring System, and Manchester Scoring System). The authors suggested that albumin and LDH levels might be used in the risk scoring in further studies. Further studies demonstrated that serum albumin level was a critical prognostic factor in the lung cancer (Forrest et al., 2003; Kasymjanova et al., 2010; Leung et al., 2012; Trape et al., 2012; Gagnon et al., 2013; Jafri et al., 2013; Ulas et al., 2014). In these studies, prognostic risk models were created using a number of clinical and laboratory variables and low serum albumin level was found to be one of the poor prognostic factors in the majority of the scoring systems. With the introduction of recent findings, the Glasgow Prognostic Score (GPS) and the Advanced Lung Cancer Inflammation Index (ALI) on the basis of serum albumin and CRP level have been developed. In addition, further scoring systems such as modified-GPS, Prognostic Index (PI), Adverse Prognostic Factors (APF), and the Montreal Prognostic Score (MPS) based on the performance status, CRP, tumor markers such as carbohydrate antigen (CA)-125, and inflammatory markers such as leukocycte and neutrophil/lymphocyte ratio have been developed (Forrest et al., 2003; Kasymjanova et al., 2010; Leung et al., 2012; Trape et al., 2012; Gagnon et al., 2013; Jafri et al., 2013; Ulas et al., 2014). In the majority of these studies, many patients had a metastatic disease (Forrest et al., 2003; Kasymjanova et al., 2010; Leung et al., 2012; Trape et al., 2012; Gagnon et al., 2013; Jafri et al., 2013; Ulas et al., 2014).

Clinical studies on NSCLC, a heterogeneous medical condition, date back to before 1980 (Finkelstein et al., 1986). Preliminary findings were obtained a randomized Phase III study conducted by ECOG. These findings suggested that performance status, female sex, bone, liver, and subcutaneous metastasis, the absence of symptom and weight loss, and non-large cell histology had a positive impact on survival (Finkelstein et al., 1986). In addition, further studies showed that age, cisplatin-based regimens, Karnofsky performance score, leukocytosis, hypercalcemia, neutrophilia, male sex, skin and liver metastasis, and weight loss were among the poor prognostic factors (Albain et al., 1991; Paesmans et al., 1995; Ulas et al., 2014).

Furthermore, recent studies included smoking status, serum LDH level, thrombocytosis, and CRP. However, our study was not powered to show the impact of age, sex, performance status, smoking status, neutrophilia, weight loss, LDH level, CRP, tumor degree and tumor histology on PFS and OS among the patients with Stage IIIB NSCLC. Therefore, our findings were consistent with previous study findings. However, several studies demonstrated that these factors were poor prognostic factors, while some authors reported no prognostic value (Hoang et al., 2005; Arinc et al., 2009; Kaya et al., 2013).

In this study, we included only patients with Stage IIIB NSCLC, as serum albumin level might be influenced by several factors. A number of previous studies, however, included patients with Stage III and IV NSCLC and showed that the majority of the patients had metastatic disease. None of these aforementioned studies excluded patients with hepatic dysfunction and no data were obtained on hepatic dysfunction. In addition, the number and localization of metastatic lesions and the impact of these lesions on hepatic synthesis were not discussed in these studies. However, hepatic metastasis-related hepatic dysfunction is a well-known cause of hypoalbuminemia (Maestu et al., 1997; Matsunuma et al., 2014).

Moreover, in a study, Jin et al. (2013) reported that preoperative and postoperative serum albumin levels had a significant predictive value for recurrence-free survival (RFS) in patients with Stage I NSCLC. In another study in 1984, Fatzinger et al. (1984) divided 81 patients into two groups including resectable and unresectable patients with Stage III NSCLC. The authors reported that the patients with a serum albumin level of 3.4 g/dL had a better prognosis. Despite smaller sample size, these findings are mostly consistent with our study findings.

However, there are some limitations to our study. These included relatively small sample size, retrospective study design, and heterogeneous study populations. Nonetheless, we found that the patients with a serum albumin level of 3.11 g/dL had reduced treatment response and shorter PFS and OS rates. We, therefore, believe that our study findings may be reflected to the clinical practice in terms of follow-up period and further studies. Despite small sample size for the subgroup analysis, these findings suggest that brain is the primary metastatic site among the patients with a serum albumin level of <2.11 g/dL. These findings may also shed light into the further studies investigating inflammatory, genetic, and molecular markers and be a guide for treatment selection for the patients with Stage IIIB NSCLC.

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