RESEARCH ARTICLE

Prognostic Significance of Basic Laboratory Methods in Non-Small-Cell-Lung Cancer

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Abstract

Background: In our study, the LDH, albumin, hemoglobin, neutrophile, thrombocyte, lymphocyte counts and prognostic significance of neutrophile-lymphocyte and thrombocyte-lymphocyte ratios in NSCLC derived from these counts obtained during regular examinations of patients were examined. Materials and Methods: Histopathologically diagnosed non-small-cell-lung cancer patients between 2008 and 2010 were included in the study. Before the treatment, full blood count including routine lymphocyte count, blood biochemistry examinations including liver (AST, ALT, total protein, Albumin), LDH and kidney (BUN, Cre) function tests were performed. Results: A total of 156 patients, 76 of whom (48.7%) were female and 80 of whom (51.3%) were male were included. Mean hemoglobin level was determined as 12. Overall survival was found to be significantly dependent on whether patients were anemic or not (p: 0.005). Mean LDH level was determined as 233.4. There was nosurvival difference between patients with and without high LDH (p: 0.532). In patients where NLR showed systemic inflammatory response, overall survival was 10.8 months whereas this duration was 19.6 months in patients where the systemic inflammatory response was negative (p: 0.012). In patients where TLR showed systemic inflammatory response, overall survival was 13.6 months whereas this duration was 21.9 months in patients where the systemic inflammatory response was negative (p: 0.04). Conclusions: Molecular methods have been changing rapidly in today's world and they manage the treatment besides defining the prognosis of patients. However, easily accessible and cheap laboratory parameters should be considered in the prognosis of patients besides these new methods.

Keywords: Non-small cell lung cancer - lactate dehydrogenase - albumin - inflammatory response - thrombocyte

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Introduction

Lung cancer is still the most frequent cancer in the world despite many precautions (Siegel et al., 2012). Prognosis of a lung cancer patient can vary depending on the cell type, tumor stage, molecular characteristics of the tumor such as EGFR, ALK expressions and overall performance of the patient (Kulesza et al., 2111).

In many studies about NSCLC, it has been demonstrated that laboratory examinations such as albumin, calcium, hemoglobin, lymphocyte count, lactate dehydrogenase (LDH) level, BUN, white blood count, neutrophile count have a prognostic role as well as these molecular indicators (Zhang et al., 2013).

Neutrophile Lymphocyte Ratio (NLR), Thrombocyte Lymphocyte Ratio (TLR) are indicators of systemic inflammatory response and have been demonstrated as prognostic factors in many types of cancer (McMillan et al., 2009). Prognostic importance of NLR in NSCLC has been determined (Nakahara et al., 2005).

In Stage I-III non-small cell lung cancer patients (NSCLC) curative surgery, radiotherapy and chemotherapy combinations can be used. In stage IV diseases the purpose of treatment is palliation. Laboratory parameters can be used in the determination of treatment intensity. These laboratory parameters should be cheap and easy to achieve. In our study, the LDH, albumin, hemoglobin, neutrophile, thrombocyte, lymphocyte counts and Neutrophile - Lymphocyte Ratio, Trombocyte - Lymphocyte ratio derived from these counts all of which were obtained during regular examinations of patients and their prognostic significance in NSCLC were examined.

Materials and Methods

Histopathologically diagnosed non-small-cell-lung cancer patients at Süleyman Demirel University Department of Radiation Oncology and Antalya Education and Research Medical Oncology Clinic between 2008 and 2010 were included in the study. Patients who were initially evaluated at different centers were excluded from the study. Patient files were examined retrospectively

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and the stage of disease and information about treatment were obtained. Before the treatment, full blood count including routine lymphocyte count, blood biochemistry examinations including liver (AST, ALT, total protein, Albumin), LDH and kidney (BUN, Cre) function tests were performed. Cases exhibiting a hemoglobin level lower than 12g/dl were considered as anemia. LDH values over 250U/L were considered as high LDH. Serum albumin level was determined via bromocresol purple method as the biochemical indicator of nutritional status, and values under <3.5mg/dL were considered as hypoalbuminemia. NLR was obtained by dividing absolute neutrophile number to absolute lymphocyte number. TLR was obtained by dividing absolute thrombocyte number to absolute lymphocyte number. Values such as NLR≥5 and TLR≥150 were considered as indicators of systemic inflammatory response.

Statistical analysis

Statistical analysis was done by using SPSS 15.0 software. The relation of NLR, TLR, LDH and hypoalbuminemia with survival was individually researched. Statistical differences were verified with Log-rank test. Significant p value was accepted as <0.05.

Results

A total of 156 patients of whom 76 were female (48.7%) and 80 were male (51.3%) was included in the study. The age of patients was determined as 60.4±11.5 (Table 1). 63 of the patients (40.4%) had Stage IIIA, 35 of them (22.4%) had stage IIIB, 58 (37.2%) of them had stage IV disease. When patients were evaluated according to histological sub-type of cancer, 85 of them (54.8%) had squamous cell carcinoma, 44 of them (28.2%) had adenocarcinoma, and 21 of them (13.6%) had an undifferentitated cancer. When performances of patients were evaluated based on ECOG, the score of 71 patients (45.5%) was 0, score of 70 patients (44.9%) was 1, and score of 15 patients (9.6%) was 2. Mean follow up period of patients was 12.5 months.

Table 1. Patient Characteristics

	Mean, Standard Deviation	Median	Range
Age	60.4±11.5	60	30-88
LDH (U/L)	233.4±103.2	203	95-779
HGB (g/dl)	12.0±2.2	12.3	4.1-17.5
NEU (10^3/mm^3)	7.06±3.55	6.31	1.20-28.3
LYM (10^3/mm^3)	1.93±0.96	1.79	0.16-7.4
PLT (10^3/mm^3)	347.7±139.7	321	131-986

*LDH: lactic dehydrogenase, WBC: white blood cells, PLT: platelets, HB: hemoglobin, Neu: Neutrophil

Mean survival was determined as 17.6 months (14.1-21.1 months with confidence interval).

Mean hemoglobin level of patients was determined as 12. Fourty-seven of the patients (30.1%) were considered as anemic. Survival of patients based on whether they were anemic or not were found to be significantly different (p:0.005) (Figure 1A). Mean survival of anemic patients was 11.7 months whereas Mean survival of non-anemic patients was determined as 19.3 months.

Mean LDH level was determined as 233.4. LDH value was considered as high in 49 of patients (31.4%). There were no difference of survival between the patients with and without high LDH (p 0.532) (Figure 1B). Hypoalbuminemia was detected in 42 of patients (26.9%). Hypoalbuminemic patients had significantly shorter lifetimes (p 0.001). Mean survival was detected as 9.8 months in hypoalbuminemic patients and as 20.5 months in patients with normal levels of albumin (Figure 2A). In 49 of patients (31.4%) NLR value showed systemic inflammatory response. Mean survival of patients with systemic inflammatory response according to NLR values was 10.8 whereas Mean survival of patients with no systemic inflammatory response was 19.6 months (p:0.012) (Figure 2B). Mean survival of patients with systemic inflammatory response according to TLR values was 13.6 whereas it was 21.9 months in patients with no systemic inflammatory response (p:0.04) (Figure 2C).

Discussion

In our study, we have demonstrated that levels of hemoglobin, albumin and NLR determined for routine evaluation of NSCLC patients, had prognostic significance.

Anemia is a bad prognostic factor related to short lifetime independent from the cancer type. Treatment of anemia increases the response to treatment of cancer (Caro et al., 2001; Littlewood et al., 2001). In the European Cancer Anaemia Survey study, anemia prevalence in

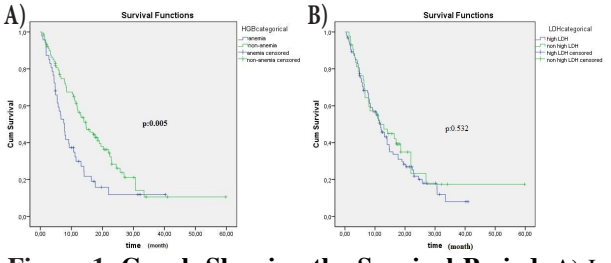

Figure 1. Graph Showing the Survival Period. A) In relation to patients based on whether they were anemic or non-anemic; and **B)** In relation to LDH categorical

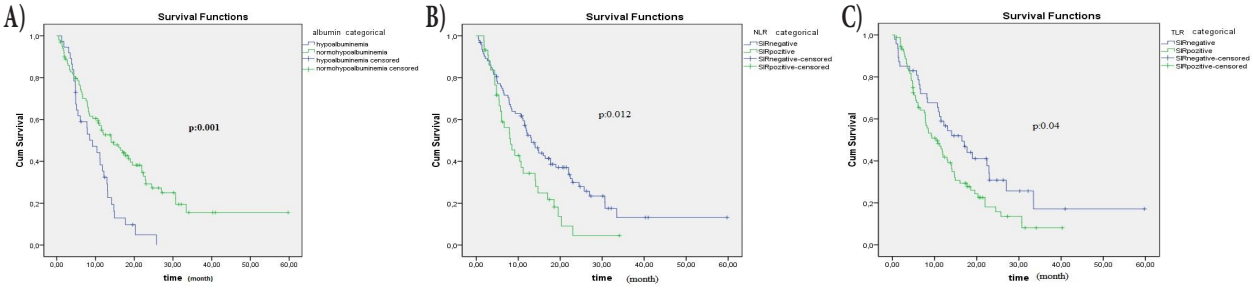

Figure 2. The Survival Period. A) Relation to normo or hypoalbuminemia; **B)** Relation to NLR; and **C)** Relation to TLR

patients with cancer was determined as 39.3% whereas this ratio was 77.0% in all patients with lung cancer and as 42.3% in non-treated patients (Ludwig et al., 2004). Since patients who were not treated previously were included in our study, our results are similar to the results of the non-treated patient group of that study. Both chemotherapy and radiotherapy increase the anemia prevalence. Although patients with anemia were treated their lifetimes were found significantly shorter than the ones without anemia. Ademuyiwa et al. also determined a similiar result in their study searching the prognostic factors in Stage III NSCLC patients (Ademuyiwa et al., 2007). In that study, median survival was determined as 16.8 months in anemic patients whereas it was 21.5 months in non-anemic patients. Anemia is a prognostic factor not only for the patients undergoing first step treatment, but also for patients receiving 2nd and 3rd step treatments. For instance, in patients receiving second and third step Gefitinib treatment, it was demonstrated that anemia was a bad prognostic factor (Pircher et al., 2011).

LDH is the enzyme catalyzing the lactate formation reaction on pyruvate. LDH level in cancer cells indicates the increase of glycolytic activity and the decrement of oxygen dependency of cells. Increased LDH level is related to intratumoral hypoxy and acidity is related to aggressive tumor structure. Increase in LDH level indicates the increase in the lactic acid production and pH decrement of the extracellular fluid consequently. It has been demonstrated that it increases the acidic pH gelatinized activity and cathepsin D production (Vaupel et al., 2001). Increase in gelatinase activity contributes to the invasion of tumor (Rozhin et al., 1994). It has been demonstrated that LDH increase is related to bad prognosis in many cancer types and NSCLC (Koukourakis et al., 2003). In our study, no relation was found between LDH increment and prognosis.

Nutritional status is considered as a part of the disease and treatment in many lung cancer patients (Bagan et al., 2013). In majority of NSCLC patients, malnutrition and hypoalbuminemia are observed (Bashir et al., 1990). In our study, we have demonstrated that the survival of hypoalbuminemic patients was lower. In a study where the prognostic factors in NSCLC patients developing radiation pneumonia were evaluated, it has been demonstrated that radiation pneumonia reaching outside the radiotherapy treatment area and albumin level lower than 3.5 g/L were related to short survival (Wang et al., 2002). In a study examining the prognostic significance of plasma IGF-I in 77 metastatic NSCLC patients, it has been determined that IGF-I level in patients over the age of 70 and exhibiting a tumour with squamous histology was lower. In the same study a correlation between IGF-I levels and albumin and CRP values was also found. It has been determined that serum albumin values were related to the period till the progression and overall survival (Vlachostergios et al., 2011). Low pre-albumin levels that are early indicators of hypoalbuminemia are also the indicators of early recurrence and bad prognosis in early stage NSCLC patients undergoing surgery (Kawai et al., 2012). Hipoalbuminemia causes more side effects with chemotherapeutics along with shorter survival (Arrieta et al., 2010).

In our study, NLR and PLR were used as systemic inflammatory response indicators. NLR and PLR are frequently used as systemic inflammatory response indicators (McMillan et al., 2009). It has been demonstrated that NLR has a prognostic role in lung, gastric, pancreas, ovary, colorectal cancers and colorectal cancer metastasis (Sharma et al., 2008). Besides its prognostic role, NLR also has a predictive role in the response to treatment. For instance, it predicts the response to sunitinib and dosetaxel treatment and it is related to the toxicity developing with gemsitabin usage (Keizman et al., 2012). It plays a role in the prediction of the response in advanced NSCLC patients receiving first step platinum based chemotherapy (Yao et al., 2013). In a study where the response to preoperative chemo-radiotherapy in local advanced rectum cancer was researched, survival was found to be lower in patients with high NLR (Carruthers et al., 2012). In a study where resected NSCLC patients were evaluated, it has been demonstrated that high NLR value was related to worse survival (Tomita et al., 2011). Similar results were obtained in the study of Sarraf et al. They argued that NLR could be used in determining high risk patients among patients without early stage adjuvant chemotherapy indication (Sarraf et al., 2009). NLR plays a role as a prognostic factor not only in early stage disease but also in local advanced and metastatic stages (Cedrés et al., 2012). Teramukai et al. have demonstrated that NLR was a prognostic factor in Stage IIIB and Stage IV NSCLC patients receiving actual chemotherapy regimes, similar to our study (Teramukai et al., 2009).

It has been demonstrated that PLR has a prognostic role in ovary and pancreas cancers (Teramukai et al., 2008). In a study where albumin NLR and PLR were evaluated, NLR was found to be statistically insignificant as a prognostic factor unlike our study, whereas PLR and serum albumin level was found to have a prognostic significance (Sánchez-Lara et al., 2012).

Today, molecular methods have been developing rapidly and they lead the treatment along with the determination of patients' prognosis. Besides these new methods, these easily reached, cheap and easy-to-use laboratory parameters should be considered while determining the prognosis of patients.

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