RESEARCH ARTICLE

Could the Neutrophil to Lymphocyte Ratio be a Poor Prognostic Factor for Non Small Cell Lung Cancers?

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Abstract

Background: Although many prognostic factors have been identified for lung cancers, new ones are needed to determine the course of the disease. Recently, a high neutrophil to lymphocyte ratio (NLR) prior to surgery or treatment has been shown to be an indicator of prognosis for cancer. The aim of this study was to investigate the value of NLR as a prognostic factor and the correlation between NLR and other probable clinical prognostic factors in non small cell lung cancer patients prior to treatment. Materials and Methods: Data of patients who were diagnosed with non-small cell lung cancer in our institution were retrospectively reviewed. Demographic and clinicopathologic characteristics were recorded. NLR was calculated before the application of any treatment. Results: A total of 299 patients, 270 (90%) males and 29 (10%) females, were included in the study. Age (p<0.001) stage (p<0.001), Eastern Cooperative Oncology Group performance status (p<0.001), weight loss (p<0.001), anemia (p<0.001), histopatology (p<0.001), NLR ≥3 (p=0.048), NLR ≥4 (p=0.025) and NLR ≥5 (p=0.018) were found to be the prognostic factors. Age, anemia, Eastern Cooperative Oncology Group performance status, the stage, NLR (≥5) were an independent prognostic factors. There was a positive correlation between NLR and the Eastern Cooperative Oncology Group performance status (0.23, p=0.001), the C reactive protein levels (r=0.36, p<0.001). Conclusions: Prior to treatment high NLR was found as an independent poor prognosis factor. Besides, NLR correlated with Eastern Cooperative Oncology Group performance status and the C reactive protein levels.

Keywords: Lung cancer - neutrophil to lymphocyte ratio - prognostic factors - C reactive protein

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Introduction

Lung cancer is the leading cause of cancer related death in both men and women (Jemal et al., 2011; Siegel et al., 2013). Aproximately 85% of lung cancers are non small cell lung cancer (NSCLC). Despite the fact that efforts and progress continue in diagnoses and treatment, the prognosis of NSCLC is still poor (Jemal et al., 2011). Survival descreased progresively with more advanced disease (Goldstraw et al., 2007). Despite the fact that curative surgery is undergone, about 40% of patients will present with local recurrence or metastasis in 2 year after surgery (Mountain, 1997). Several prognostic factors such as stage, Eastern Cooperative Oncology Group performance status (ECOG PS), age, histopathology, sex, carcinoembryonic antigen (CEA) were previously reported (Gail et al., 1984; Hoang et al., 2005; Simon et al., 2005; Goldstraw et al., 2007; Riquet et al., 2007; Albain et al., 2009).

Many prognostic and predictive factors have been investigated such as Kirsten Rous sarcoma virus oncogene (K-ras), 5'endonuclease of the nucleotide excision repair complex (ERCC1), echinoderm microtubule associated protein like-4 and anaplastic lymphoma kinase (EML4-ALK) and epidermal growth factor receptor (EGFR) (Simon et al., 2005; Olaussen et al., 2006; Takahashi et al., 2010; D'Angelo et al., 2012). Still the most important prognostic factors are stage and PS (Cedres et al., 2012). Although many prognostic factors have been identified for lung cancers, new ones are needed to determine the course of the disease.

It is increasingly recognized that the host systemic inflammatory response seems to be critical role in the development and progression of many cancers. Some studies have identified the relationship between neutrophils and tumor angiogenesis, cancer cell proliferation, tumor metastasis, tumor response to the treatment (Coussens and Werb, 2002; Mantovani et al., 2008). Neutrophil/lymphocyte ratio (NLR) imbalance was thought to be secondary to tumor hypoxia or necrosis and related with antiapoptosis (Roxburgh and McMillan, 2008). Elevated NLR may be an indicator of systemic inflammation and also an indicator of poor prognostic factor for NSCLC prior to surgery or systemic treatment like the many types of solid cancers (Walsh et al., 2005; Halazun et al., 2008; Kao et al., 2010; Cedres et al., 2012; Dirican et al., 2013;

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Kaya et al., 2013; Uslu et al., 2013).

There are two objectives of this study; the first, to investigate the value of peripheral blood NLR as a prognostic factor in NSCLC patients prior to treatment, and the second, to investigate the correlation between NLR and gender, age, ECOG PS, disease stage, level of hemoglobin, biomedical parameters (lactate dehydrogenase (LDH) and CEA level) and the histopathologic type.

Materials and Methods

Patients who were diagnosed with NSCLC in our institution were retrospectively reviewed. Demographic and clinicopathologic characteristics of the patients were recorded by using hospital records and computer data system.

Prior to treatment, each patient's PS was scored according to the Eastern Cooperative Oncology Group Scoring System. Stage of disease was evaluated according to the 2010 TNM classification developed by the International Union Against Cancer and the American Joint Committee on Cancer.

Patients with a haemoglobin level below 12 g/dl for anemia were included in this study. Peripheral blood samples were recorded at baseline, prior to any treatment. NLRs were calculated before the application of any treatment. Although some reports have showed that neutrophil to lymphocyte ratio could be used as a predictor before treatment and a predictor of response to treatment, there is yet no precisely defined cut-off value. Thus patients were stratified according to their NLRs of patients with NLR <2.5 *vs* ≥2.5, and <3 *vs* ≥3, and <4 *vs* ≥4, and <5 *vs* ≥5.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 15.0 for Windows; SPSS, Chicago, IL, USA). Medians, and frequencies were calculated for patient demographics. Survival analysis was performed according to the Kaplan-Meier method. Survival curves were compared with the log-rank test. Multivariate analysis with Cox regression models was used to assess the independent factors that have an effect on survival. Sperman test was used to assess the correlation between NLR and gender, age, ECOG PS, disease stage as well as the level of hemoglobin, biomedical parameters (LDH and CEA level) and the histopathologic type. p≤0.05 was considered to indicate statistical significance.

Results

Table 1 summarizes the patients' demographic and clinical characteristics. The patients were 270 (90%) men and 29 (10%) women. Their median age at time of cancer diagnosis was 61 years (range, 31-82).

Due to the lack of a defined NLR, patients were described according to their NLRs of patients with NLR <2.5 *vs* ≥2.5, and <3 *vs* ≥3, and <4 *vs* ≥4, and <5 *vs* ≥5. The 1-year, 2-years and the median overall survival (OS) of patients with NLRs of ≥3 (p=0.048), ≥4 (p=0.025) and ≥5 (p=0.018) were affected significantly in univarited analysis. Table 2 shows the 1-year, 2-years and the median OS of patients according to NLRs. OS curve of patients with NLR <5 and ≥5 is shown in Figure 1. Furthermore, age (p<0.001) stage (p<0.001), ECOG PS (p <0.001), weight loss (p<0.001), the presence of anemia at diagnosis (p<0.001), histopatology (p<0.001) were found to be the prognostic factors for survival in univariated analysis (Table 3). In multivariated analysis, age, the presence of anemia at the diagnosis, ECOG PS, the stage, NLR (≥5)

Table 1. Clinical and Demographic Characteristics

		No. of patients	%
Gender	Male	270	90
	Female	29	10
Age	<65 years	196	66
	≥65 years	103	34
Comorbid Disease	Yes	131	44
Weight loss	Yes	126	42
ECOG PS*	ECOG 0	134	45
	ECOG 1	98	33
	ECOG 2	48	16
	ECOG 3	19	6
Anemia	>12 g/dl	134	43
	≤12 g/dl	165	57
Stage	I	25	8
	II	24	8
	III	135	45
	IV	115	39
Histopathology	Squamous cell	124	41
	Adenocarcinoma	71	24
	NOS**	104	35

*ECOG PS: the Eastern Cooperative Oncology Group performance status; **NOS: not otherwise specified

Table 2. The 1 Year, 2 Years and the Median OS of Patients According to NLRs

Univariate analysis		The 1-year OS* (%)	The 2-years OS (%)	Median OS (month)	p value
NLR**	<2.5	69	26	14	0.183
	≥2.5	42	24	9	
NLR	<3	66	26	14	0.048
	≥3	39	23	8	
NLR	<4	56	29	13	0.025
	≥4	35	21	8	
NLR	<5	55	29	13	0.018
	≥5	35	34	7	

*OS: overall survival; **NLR: neutrophil to lymphocyte ratio

Table 3. Prognostic Factors in Univarite Analysis

Univariate analysis		1-year OS* (%)	2-years OS (%)	Median OS (month)	p value
Age	<65 years	62	36	17	<0.001
	≥65 years	64	24	10	
ECOG PS**	ECOG 0	75	51	26	<0.001
	ECOG 1	54	24	13	
	ECOG 2	30	6	6	
	ECOG 3	-	-	2	
Weight loss	No	65	37	17	<0.001
	Yes	45	24	10	
Histopathology	Squamous cell	58	37	13	<0.001
	Adenocarcinoma	67	39	17	
	NOS***	47	18	10	
Stages	Stage I	96	76	51	
	Stage II	79	65	36	<0.001
	Stage III	62	33	14	
	Stage IV	34	6	8	
Hemoglobin	<12 g/dL	54	20	13	<0.001
	≥12 g/dL	69	28	23	

*OS: overall survival; **ECOG PS: the Eastern Cooperative Oncology Group performance status; ***NOS: not otherwise specified

Table 4. Independent Prognostic Factors in Multivariate Analysis

Multivariate analysis	p value	Hazard ratio	95%CI*
Age (≥65 years)	0.049	1.6	1.0-2.5
Anemia at the diagnosis	0.004	0.5	0.4-0.8
ECOG PS[2]	0.003		
ECOG 1 *vs* ECOG 0	0.029	1.7	1.1-2.7
ECOG 2 *vs* ECOG 0	0.013	2.5	1.2-5.0
ECOG 3 *vs* ECOG 0	0.001	5.1	2.0-13.1
Stage	<0.001		
Stage II *vs* stage I	0.348	1.9	0.5-6.9
Stage III *vs* stage I	0.011	4.8	1.4-15.9
Stage IV *vs* stage I	0.002	7.4	2.1-25.6
NLR (≥5)	0.017	1.7	1.0-2.7

*CI: confidence interval

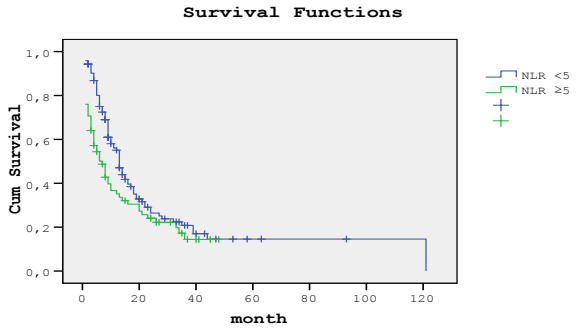

Figure 1. The Survival Curve According to NLR <5 *vs* ≥5

were an independent prognostic factors.

NLRs were correlated with gender, age, patients' ECOG PS, disease stage as well as the level of hemoglobin, biomedical parameters (LDH and CEA level) and the histopathologic type. There was a significant correlation between ECOG PS and NLR (r=0.227, p=0.001). A significant positive correlation was observed between the CRP levels and NLR (r=0.36, p<0.001). No significant correlation was calculated between NLR and patients' gender, age, comorbidity, disease stage, the level of hemoglobin, histopathologic type, LDH, CEA levels.

Discussion

It is well known that chronic inflammation predisposes to various types of cancer (Uslu et al., 2013). On the other hand, inflammation can cause tumor proliferation and survival in patients with malignancy (Schmidt et al., 2005). After understanding the relationship between inflammation and malignancy, the prognostic value of cancer-related inflammatory response becomes a current issue for oncology practise.

A number of studies in the last two decades have suggested an association between the neutrophil count or NLR and the prognosis of cancer patients (Gail et al., 1984; Simon et al., 2005; Olaussen et al., 2006; Mantovani et al., 2008; Roxburgh and McMillan, 2008; Albain et al., 2009; Teramukai et al., 2009; Kao et al., 2010; Takahashi et al., 2010; Cedres et al., 2012; D'Angelo et al., 2012), although no acceptable explanations for the mechanisms underlying these observed associations have been proposed. It may be associated lymphopenia or increasing numbers of neutrophils and monocytes (Donnem et al., 2010). Lymphocytes play a critical role in cell mediated antitumor immune response in various cancers (Halazun et al., 2008; Kao et al., 2010; Zhang et al., 2013). Activated specific CD8(+) T cells can control tumor growth by cytotoxic activity and inducing apoptosis of tumor cells (Leitch et al., 2007; Schmidt et al., 2007; Zhang et al., 2013). In the other hand neutrophilia often accompanies the diagnosis of cancer. The causes of neutrophilia in cancer patients are not fully understood, and are likely to be the result of a combination of factors. One obvious cause of neutrophilia is paraneoplastic production of myeloid growth factors by cancer cells themselves. Other possible factors that cause neutrophilia are coexistent infection and cancer-related inflammation (Teramukai et al., 2009). Furthermore, many acute inflammatory blood markers, including C-reactive protein (CRP), leukocytes, albumin, interleukin-6 (IL-6), LDH were identified for lung cancer prognosis (Donnem et al. 2010; Kasymajanova et al., 2010; Zikos et al., 2011; Zhang et al., 2013).

Prognostic and predictive role of NLR were invesigated in many cancers (Gondo et al., 2012; Mano et al., 2013; Unal et al., 2013; Yucel et al., 2013; Zheng et al., 2013). And various values of NLR were found important in these studies. Gondo et al. showed that NLR ≥2,5 was an independent prognostic factor for bladder cancer (Gondo et al., 2012). Mano et al. showed that NLR ≥2,81 was factor of an independent predictive survival after hepatectomy in patients with hepatocellular carcinoma (Mano et al., 2013). In another study, it was found that high baseline NLR (NLR ≥4) was associated with worse OS for patients with advanced hepatocellular carcinoma (Zheng et al., 2013). Yao et al. reported that a high pretreatment NLR ≥2.63 was an independent risk factor for progression free survival (PFS) and OS in patients with NSCLC (Yao et al., 2013). In another study performed by Unal et al., pretreatment high NLR (NLR ≥3, 44) was associated with significantly shorter DFS and OS in patients with NSCLC (Unal et al., 2013). Thus, they suggested that pretreatment NLR could provide important prognostic results in patients with NSCLC and also predict the treatment response. NLR ≥5 have been shown as a prognostic and predictive marker in different types of cancer patients. Some studies have showed that NLR ≥5 is an independent predictor of recurrence and poor survival in patients with colorectal cancer (Walsh et al., 2005; Halazun et al., 2008; Chua et al., 2011). Kao et al. demonstrated NLR ≥5 was a predictor of shorter survival for mesotelioma (Kao et al., 2010). Recently, Yucel et al. have showed that patients with NLR >5 have poor prognosis in neuroendocrin tumors (Yucel et al., 2013).

In this study, we stratified patients according to their NLR of patients with NLR <2.5 *vs* ≥2.5, and <3 *vs* ≥3, and <4 *vs* ≥4, and <5 *vs* ≥5. The 1-year, 2- years and the median OS of the patients with NLRs of ≥3, ≥4, ≥5 were statistically worse affected than the patients with NLRs of <3, <4, and <5. These factors were found as a prognostic factors, moreover, NLR ≥5 was only found as an independent prognostic factor.

Anemia, weight loss and ECOG PS are well known prognostic factors (Wigren, 1997). Patients with nutritional problems and weight loss may progress to malnutrition. The progress of the current status facilitates

both accelerated formation anemia and a deterioration of the performance status as a systemic inflammatory response (Scoot et al., 1996; Sanchez-Lara et al., 2012; Shintani et al., 2012). Due to having comorbid diseases in most of the elderly patients with NSCLC, treatment complications could be more. Thus, prognosis of elderly patients with NSCLC is worse than the younger ones (Gore et al., 2012). It is known that histological subtypes of NSCLC influence the survival. Charloux et al. evaluated the impact of NSCLC histological subtypes of NSCLC on survival, and they showed that the prognosis of the patients with bronchioloalveolar carcinoma was better than the others (Charloux et al., 1997). Ferguson et al., in a series of 478 lung cancer patients, found women to have longer survival and they concluded that gender is an independent prognostic factor (Ferguson et al., 1990). Similiarly, Shinkai et al. (1992) and Paesmams et al. (1995) showed that survival of female patients were longer than males. They indicated that gender is an independent prognostic factor (Shinkai et al., 1992; Paesmans et al., 1995). In contrast, there are various studies showing no prognostic effect of sex on prognosis (Martins and Pereira, 1999; Caglayan et al., 2004). It is known that stage is the most important prognostic factor for NSCLC (Cedres et al., 2012). In lung cancer previous reports had evaluated the association between NLR and outcome. According to Sarraf et al. (2009) the preoperative NLR was associated with higher stage and it was an independent prognostic factor for patients undergoing complete resection for NSCLC (Sarraf et al., 2009). In one study performed by Teramukai, the impact of NLR was examined. They showed that pretreatment neutrophil count was associated with short OS and PFS (Teramukai et al., 2009). In Cedres et al. (2012) study, prognostic factors such as histological subtype and gender, patients with NLR ≥5 presented a decrease in overall OS. In addition, they showed that patients with NLR <5 had better survival (Cedres et al., 2012).

In current study, similar to other studies, the 1 and 2-years OS of patients with advanced age (≥65 yeras), high ECOG PS score, weight loss, NOS histopatology, advanced stage, the presence of anemia at the diagnosis, high NLR were effected stastically worse. In multivariated analysis, we found that advanced age, anemia at the diagnosis, high ECOG PS score, advanced stage, and high NLR (≥5) were poor independent prognostic factors.

In the literature, there are very few correlation studies of NLR. Cedres et al. detected increasing stage was associated with increasing NLR. They reported that patients with T4 and N3 presented significantly higher NLR than patients with T1 and N0. Thus, they showed the association of NLR ≥5 and poor prognosis in advanced NSCLC. CRP is a nonspecific serum marker of acute phase inflammatory response and LDH is the enzyme catalyzing the lactate formation reaction on pyruvate. Increased CRP level and LDH are related to intratumoral hypoxia and hypoxia can cause systemic inflammatory response. Thus, increased CRP level and LDH are related to bad prognosis in many cancers and NSCLC (Vaupel et al., 2001; Heikkila et al., 2007). In this study, we could not find CRP and LDH as a prognostic factors. Furthermore, there was a significant positive correlation between NLR and the level of CRP, ECOG performance status score but not with gender, age, stage, the level of LDH, the level of CEA, the level hemoglobin, histopathology.

As a result, age, the stage, ECOG PS, the presence of anemia at diagnosis, weight loss, histopathology, NLR ≥3, NLR ≥4 and NLR ≥5 were found to be the prognostic factors for survival. Moreover, NLR ≥5 was found as an independent prognostic factor. There was a significant positive correlation between the NLR, CRP level and ECOG PS. NLR is an inexpensive, easily avaliable blood test and it may be a useful prognostic indicator in lung cancer that does not require any additional resources for rouine use.

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