RESEARCH ARTICLE

Prognostic Value of the Neutrophil to Lymphocyte Ratio (NLR) in Lung Cancer Cases

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Abstract

Haemogram assessment is a cheap and easy method which can be readily performed for almost all patients. Leucocyte, neutrophil and lymphocyte counts and the neutrophil to lymphocyte ratio (NLR) are markers of systemic inflammation. We here aimed to evaluate haemogram parameters of our patients with lung cancer according to the pathologic diagnosis of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). **Materials and Methods:** The study included 386 patients diagnosed with lung cancer in our hospital between January 2006 and January 2014. A retrospective examination was made of the data from the patient records and the hospital information. NLR values were categorised into two groups: <3 and ≥3. **Results:** Median survival time in patients aged <65 years was 28.7 months and in those aged ≥65 years, it was 18.4 months (p<0.001). The median survival time was 20.2 months in NSCLC and 13.0 months in SCLC patients (p<0.001). In NSCLC cases with NLR<3 the median survival time (31.1 months) was longer than that of patients with NLR≥3 (18 months) (p=0.003). In SCLC patients, no relationship could be found between NLR and median survival time (p=0.408). With every 1 unit increase in lymphocyte count a 5.5% decrease in risk of periodic death ($(1/0.947)\times100 = 5.5\%$) was noted. **Conclusion:** The results of this study demonstrated that lymphocyte count, neutrophil count, Hb, Htc, and NLR are useful in determining prognosis in lung cancer (LC) patients and NLR could be more significant in determining the prognosis in NSCLC than in SCLC cases.

Keywords: Lung cancer- haemogram- neutrophil to lymphocyte ratio (NLR)

Introduction

Lung cancer (LC) is still the most frequently diagnosed cancer type and the leading cause of cancer-related deaths. Its incidence worldwide is increasing cumulatively. Despite all therapeutic options, five-year survival rates are low. Pathologically, 85% of the total cases are non-small cell lung cancer (NSCLC) and 15% are small cell lung cancer (SCLC) (Herbst et al., 2008). Haemogram measurement is a cheap and easy method which is performed in almost all patients. Leukocyte, neutrophil and lymphocyte count and neutrophil to lymphocyte ratio (NLR) are markers of systemic inflammation that are known to play main roles in cell-mediated destruction of cancer cells (Kobayashi et al., 2010). In recent studies, it has been shown that NLR and platelet to lymphocyte ratio (PLR) has prognostic value in many cancer types. In NSCLC patients, NLR, an early marker of global inflammation, has been shown to have prognostic value in determining survival (Tomita et al., 2011, Lee et al., 2012, Kaya et al., 2013, Kacan et al., 2014). Patients with higher systemic inflammation at diagnosis may have more aggressive disease and should

be treated promptly and potently, while an increasing NLR during treatment may be a precursor of disease progression and treatment failure (Derman et al., 2017).

The prognostic value of inflammatory markers, including NLR and PLR, is not well understood in SCLC (Kang et al., 2014) and the prognostic role of factors mentioned above in patients with SCLC remains controversial. However elevated peripheral NLR before treatment was an independent prognostic factor of poor progressive free survival and overall survival in SCLC patients (Deng et al., 2017).

The aim of the current study was to evaluate the haemogram parameters of patients with lung cancer according to the pathological diagnosis of SCLC and NSCLC.

Materials and Methods

A retrospective evaluation was made of 386 patients diagnosed with LC in our hospital between January 2006 and January 2014. Clinicopathological information was recorded retrospectively from hospital data. A record was

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made of patient age, gender, performance status (Ecog: The scale was developed by the Eastern Cooperative Oncology Group), haemogram parameters (leukocyte count, neutrophil count, lymphocyte count, platelet count, haemoglobin value (Hb), red blood cell distribution width (RDW), hematocrit (Htc), MPV, NLR) at initial diagnosis, the date of diagnosis, pathological diagnosis, tumor stage, treatment, progression, last visit date, and exitus date of patients who died.

Pathological (p) TNM staging was recorded for all patients based on the AJCC/UICC TNM classification, 7th edition.

The haemogram parameters were assayed in the biochemistry laboratory with an Abbott Cell dyn 3700 unit, using the laser and impedance method for WBC and sub-parameters, the photometric method for Hb and the impedance method for PLT and sub-parameters.

The NLR ratio was obtained from the absolute neutrophil count and the absolute lymphocyte count. Similar to previous studies, a value of NLR ≥3 was evaluated as a potential prognostic parameter. The NLR values were categorised into two groups as <3 and ≥3.

Approval for the study was granted by the Local Ethics Committee.

Statistical Analysis

Statistical analyses were performed using SPSS® for Windows®, version 18.0 (SPSS Inc., Chicago, IL). Descriptive statistics were reported as percentage, mean, standard deviation and median values.

Distribution of data was assessed using the One-sample Kolmogorov-Smirnov test. Differences between numeric variables of two groups were tested with the Independent samples Student's t-test for continuous variables displaying normal distribution and the Mann-Whitney U test for continuous variables not displaying normal distribution. Survival rates were calculated with the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. Independent variables predicting survival were evaluated using the Cox proportional hazards model, including all variables with a value of $p < 0.20$ in the univariate analysis. The 95% confidence interval was calculated for all hazard ratios (HRs) in the Cox regression analysis. A two-tailed $p < 0.05$ was considered statistically significant.

Results

The mean age of the patients was 60.12± 9.2 years, 88.9% were male and 94.6% had a smoking history. Characteristics of the patients are shown in Table 1. Median survival time in patients <65 years (28.65 months) was longer than that of patients aged ≥65 years (18.39 months). This result was stastistically significant (p<0.001). The median survival time was 20.24 months in NSCLC and 12.95 in SCLC patients (p<0.001). In patients with NLR<3 the median survival time (31.08 months) was longer than that of patients with NLR≥3 (18 months). This result was stastistically significant (p=0.003) No relationship was found between performance status (Ecog)

Table 1. Evaluation of Patients According to Lung Cancer Diagnoses

	N	Percentage
Type 1		
Adenocarcinoma	107	27.7
NOS (not otherwise specified)	80	20.7
Squamous cell	118	30.5
Small cell	75	19.4
Large cell	6	1.5
Type 2		
Small cell cancer (SCLC)	75	19.5
Non small cell cancer (NSCLC)	311	80.5
Stage		
1a	1	0.2
1b	27	6.9
2a	14	3.8
2b	19	5.2
3a	65	17.7
3b	45	12.2
4	130	35.3
Limited stage	30	7.3
Extensive-stage	45	12.2
Treatment of radiotherapy		
Yes	62	16.0
No	324	84.0
Treatment of chemotherapy		
No	76	19.7
Yes	310	80.3
Mean±SD:4.2±1.4 Median:4 least:1 most:11		
Progression		
No	265	68.7
Yes	121	31.3
Result		
Alive	136	35.3
Deceased	250	64.7

and survival (Table 2).

In patients aged ≥65 years, Risk of periodic death was 1.567 times more than of those aged <65 years (95% CI: 1.185-2.074). The risk of periodic death in patients with SCLC and not otherwise specified (NOS) were 1.675 and 2.334 times more than those with lung adenocarcinoma. The risk of periodic death rate in patients with stage 4 and extensive disease was 2.198 times more than those with stage 3 and limited disease (95% CI: 1.6666-2.900).

With every 1 unit increase in lymphocyte count was seen to cause a 5.5% decrease in risk of periodic death ((1/0.947)x100=5.5%).

With every 1 unit increase in Hb value was seen to cause an 11.3% decrease in the risk of periodic death ((1/0.898)x100=11.3%) (Table 3).

In NSCLC patients, the median survival time in those with NLR <3 (34.76 months) was longer than that of

Table 2. Comparison of the Median Survival Time of Patients According to the Basic Characteristics

Group	Median	95% confidence	interval	P
Gender				
Male	22.73	19.26	26.2	0.979
Female	29.07	12.18	45.97	
Age				
≤64	28.65	22.23	35.06	<0.001
≥65	18.39	13.19	22.99	
Cigarette				
No	19.12	15.33	22.91	0.422
Yes	31.34	12.68	50	
Progression				
No	23.49	15.25	31.73	0.292
Yes	22.66	21.19	24.14	
Type 1				
Adenocarcinoma	34.3	25.93	42.66	<0.001
Nos	14.09	10.47	17.72	
Squamous cell	36.79	19.43	54.16	
Small cell	12.94	6.18	19.71	
Stage				
≤3 + limited stage	43.99	30.12	57.86	<0.001
4 + extensive stage	12.95	10.47	15.42	
Type 2				
SCLC	12.95	8.22	17.67	<0.001
NSCLC	25.85	20.24	31.47	
NLR				
<3	31.08	26.64	38.52	0.003
≥3	18	14.94	21.07	
ECOG (Performance status)				
0	23.00	17.96	28.03	0.391
1	21.00	15.1	26.95	
2	9.00	0.01	28.4	

NLR, Neutrophil to lymphocyte ratio; SCLC, Small cell cancer; NSCLC, Non small cell cancer; Ecog, Eastern Cooperative Oncology Group

Table 3. Evaluation with Cox Regression Analysis of the Factors Affecting the Hazard Ratio of The Patients

Group					95%	CI
	n	β	p	HR	Min	Max
Age						
<64 (Ref)	240	0.45	0.003	1		
≥65	112			1.568	1.163	2.112
Type						
Adeno cell (Ref)	99			1		
Nos	76	0.517	0.008	1.677	1.147	2.452
Squamous cell	106	-0.142	0.457	0.868	0.596	1.262
Small cell	71	0.818	<0.001	2.265	1.549	3.313
Stage						
≤3+limited (Ref)	190	0.813	<0.001	1		
4+common	162			2.254	1.709	2.972
NLR						
<3 (Ref)	160	0.303	0.031	1		
≥3	192			1.354	1.028	1.783
ECOG						
0 (Ref)	258					
1	88	0.107	0.528	1.112	0.799	1.549
2	6	-0.001	0.999	0.999	0.363	2.749
Hb	386	-0.119	0.008	0.898	0.813	0.97
L	386	-0.055	<0.001	0.947	0.919	0.976

Hb, Haemoglobin; L, Lymphocyte; NLR, Neutrophil to lymphocyte ratio; Ecog, Eastern Cooperative Oncology Group

developed and developing countries and remains the leading cause of cancer- related deaths worldwide (Siegel et al., 2013; Jemal et al., 2011). It is more frequent in males and is associated with smoking. Pathologically it is divided into NSCLC and SCLC. It has been reported that 85% of lung cancers are NSCLC (Siegel et al., 2011) and in this study, this percentage was 80%. The mean age of LC is 60 years (range, 57- 68 years) (Peng et al., 2015) and the age at diagnosis was similar in the current study patients. Age, gender, weight loss, performance status, plasma lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA) levels of the patient, stage and histopathological type of the disease are known to play an important role in prognosis (Gail et al., 1984; Hoang et al., 2005; Simon et al., 2005; Riquet et al., 2007; Albain at al., 2009). In this study, the median survival time in patients aged <65 years was 28.65 months and in those aged ≥65 years, it was 18.39 months (p<0.001). In patients aged ≥65 years, the risk of periodic death was 1.567 times more than that

patients with NLR ≥3 (19.12 months). This result was stastistically significant (p=0.002). In NSCLC patients, no relationship was determined between NLR and median survival time (p=0.408) (Table 4).

NLR has been found 3.94 for Ecog is 0, 4.2 for Ecog is 1, 3.6 for Ecog is 2. There was no statistically significant difference (p= 0.417).

The RDW, Hb and Htc values were statistically more significant in SCLC patients than in NSCLC patients (p<0.05). No statistically significant difference was found between SCLC and NSCLC patients in respect of lymphocyte and neutrophil percentages, leukocyte, platelet, MPV and NLR (p>0.05).

Discussion

LC is an important cause of mortality in both

Table 4. Comparison of Median Survival Time of Patients According to the Basic Characteristics

Group	NLR	N	Median	95%	CI	P
SCLC	<3	36	13.5	2.99	24.01	0.408
	≥3	39	10.65	4.28	16.95	
NSCLC	<3	136	34.76	24.09	45.42	0.002
	≥3	167	19.12	14.44	23.80	

SCLC, Small cell cancer; NSCLC, Non small cell cancer; NLR, Neutrophil to lymphocyte ratio; N, Neutrophil

of those aged <65 years. The median survival time in NSCLC was longer than in SCLC patients (p<0.001). In stage 4 LC patients mortality risk was high as expected (2.198 fold greater). No relationship was found between performance status (Ecog) and survival.

The relationship between systemic inflammation and cancer has been previously shown. Inflammation is known to promote tumor development and angiogenesis, and inhibit apoptosis (Coussens and Werb, 2012). Inflammation has been reported to increase the risk of various cancers, such as liver cancer, colorectal cancer, pancreatic carcinoma and lung cancer (Shim et al., 2005). Some systemic inflammation markers have been found to be correlated to the clinicopathological features of tumor patients. It has been suggested that neutrophils, as well as T and B lymphocytes play a prominent role in tumor inflammation and immunology (Lin et al., 2012; Schreiber et al., 2011). In breast, esophagus, colon, stomach and lung cancer, elevated NLR measured from peripheral blood is an independent prognostic factor (Walsh et al., 2005; Sharaiha et al., 2011; Noh et al., 2013; Sarraf et al., 2009). NLR is an inexpensive, reproducible and widely available blood test. In the current study patients with NLR<3 median survival time (31.08 months) was more than those with NLR≥3 (18 months) (p<0.003). In previous studies, it has been shown that high neutrophil count and NLR in LC patients before treatment is associated with a poor prognosis (Paesmans et al., 1995; Teramukai et al., 2009). Recently, an increasing neutrophil count has also been identified as an independent predictor of death in patients with surgically-treated NSCLC and more controversially, in advanced NSCLC (Sarraf et al., 2009; Paesmans et al., 1995; Teramukai et al., 2009; Sakai et al., 2011). NLR has been associated with poor prognosis in stage 4 NSCLC patients (Cedres et al., 2012). In tumor resectable NSCLC patients, a relationship has been shown between high NLR levels at the time of diagnosis and short survival (Sarraf et al., 2009; Paesmans et al., 1995; Teramukai et al., 2009; Sakai et al., 2011; Cedres et al., 2012; Tomita et al., 2011). NLR at initial diagnosis is a readily available and effective measurement that reflects the prognosis in SCLC patients (Kang et al., 2014).

In the current study patients with NLR<3, median survival time (31.08 months) was significantly longer than that of those with NLR≥3 (18 months) (p=0.002). In SCLC patients, no relationship could be found between NLR and median survival time (p=0.408).

A high NLR indicates an increased neutrophil count and/or a decreased lymphocyte count, as well as relative lymphopenia. Lymphocytes have a crucial role in tumor defence by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration (Coussens and Werb 2002; Mantovani et al., 2008).

A low lymphocyte count was an independent unfavorable prognostic factor of disease-free survival in patients with NSCLC (Zhang et al., 2013). Low lymphocyte count was also related with lymphatic invasion and recurrence of NSCLC but the peripheral neutrophil count had no impact on survival (Zhang et al., 2013). In this study, the lymphocyte count of surviving patients was higher but the neutrophil count was lower

than of those who died. With every 1 unit increase in lymphocyte count caused a 5.5% decrease in risk of periodic death ((1/0.947)x100=5.5%).

Anemia has been previously shown to be an independent prognostic factor for the survival rate of cancer patients (Sheikh and Littlewood 2010) and its presence is associated with decreased survival in almost all cancer types that have been studied (Caro et al., 2001). Anemia also plays a role in the prognosis of LC patients. In the current study, the Hb and Htc values in patients who survived were significantly higher than in those who died. It was also found that with every 1 unit increase in Hb value, there was a decrease of 11.3% in the risk of periodic death ((1/0.898)x100=11.3%).

Limitations of this study can be considered to be that it was retrospective and there was an inequality in the SCLC and NSCLC patient numbers.

In conclusion, the results of this study demonstrated that lymphocyte count, neutrophil count, Hb, Htc, and NLR are useful in determining prognosis in LC patients and NLR could be more significant in determining the prognosis in NSCLC than in SCLC patients.

Disclosure

The authors have no conflict of interests to declare.

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