RESEARCH ARTICLE

A New Inflammatory Prognostic Index, Based on C-reactive Protein, the Neutrophil to Lymphocyte Ratio and Serum Albumin is Useful for Predicting Prognosis in Non-Small Cell Lung Cancer Cases

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Abstract

Purpose: We aimed to establish an inflammatory prognostic index (IPI) in early and advanced non-small cell lung cancer (NSCLC) patients based on hematologic and biochemical parameters and to analyze its predictive value for NSCLC survival. **Materials and Methods:** A retrospective review of 685 patients with early and advanced NSCLC diagnosed between 2009 and 2014 was conducted with collection of clinical, and laboratory data. The IPI was calculated as C-reactive protein × NLR (neutrophil/ lymphocyte ratio)/serum albumin. Univariate and multivariate analyses were performed to assess the prognostic value of relevant factors. **Results:** The optimal cut-off value of IPI for overall survival (OS) stratification was determined to be 15. Totals of 334 (48.8%) and 351 (51.2%) patients were assigned to high and low IPI groups, respectively. Compared with low IPI, high IPI was associated with older age, greater tumor size, high lymph node involvement, distant metastases, advanced stage and poor performance status. Median OS was worse in the high IPI group (low vs high, 8.0 vs 34.0 months; HR, 3.5; p<0.001). Progression free survival values of the patients who had high vs low IPI were determined 6 months (95% CI:5.3-6.6) and 14 months (95% CI:12.1-15.8), respectively (HR; 2.4, P<0.001). On multivariate analysis, stage, performance status, lactate dehydrogenase and IPI were independent prognostic factors for OS. Subgroup analysis showed IPI was generally a significant prognostic factor in all clinical variables. **Conclusion:** The described IPI may be an inexpensive, easily accessible and independent prognostic index for NSCLC patients, useful for clinical practice.

Keywords: : Index- inflammatory- lung cancer- prognosis- survival

Introduction

Lung cancer leads to the most cancer deaths in the world. Almost a fifth of these deaths are due to the lung cancer (Siegel et al., 2014). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer (Devesa et al., 2015). Spite of the exceptional improving of anticancer agents including novel molecular targeted drugs such as erlotinib for chemotherapy against NSCLC, patients with advanced stage or recurrent lung cancer have a poor prognosis. In NSCLC, staging according to the the tumor-node-metastasis (TNM) system, molecular definition and histological subtype has been the most suitable clinicopathological variables for routine prognostication and treatment (Detterbeck et al., 2013). This prognostic factors have shown its importance, but ensured incomplete prognostic information as clinical outcome differ between patients in the identical prognostic factors. Therefore, new prognostic

determinants are needed to predict the clinical course of the patients' more reliably and exactly. For this reason many prognostic model has been improved in patients with NSCLC. The role of inflammation was important in tumorigenesis and inflammatory microenvironment was the necessary component in NSCLC (Rivas-Fuentes et al., 2015). C-reactive protein (CRP) increases as positive acute phase reactant, despite albumin as decreases negative acute phase reactant in cancer patients (Gulen et al., 2012). Therefore those prognostic models include inflammation markers such as Glasgow prognostic score (GPS), leukocytes count, neutrophil to lymphocyte ratio (NLR) and body mass index (Forrest et al., 2003; Leung et al., 2012; Kasymjanova et al., 2010; Trape et al., 2012; Jafri et al., 2013; Gagnon et al., 2013). The purpose of these prognostic models is to make quickly and easily evaluation about cancer prognosis in daily practice. We developed a inflammatory prognostic index (IPI) consist of (CRP), albumin and NLR that have an effect

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on survival by analyzing the prognostic importance of all baseline laboratory parameters and clinical characteristics of NSCLC patients. We aimed to research the predictive impact of this new prognostic model on survival.

Materials and Methods

This study was conducted at the Department of Chest disease in the Suleyman Demirel University, Dr Suat Seren Chest Diseases and Thoracic Surgery Training Hospital and Isparta State Hospital. The investigation was a retrospective and multicenter study. These patients were treated and received follow-up evaluations between January, 2009 and December, 2014. Clinicopathologic variables such as age, gender, performance status (PS), treatments, histopathology were recorded by an electronic medical record system. The patients' performance status were recorded according to the Karnofsky performance status scores. A total of 760 lung cancer patients were reviewed. The patients diagnosed with histologically or cytologically primary NSCLC and staged according to the TNM criteria (Vallieres et al., 2009) were included in this study. All stages of NSCLC were enrolled. Patients were excluded if they 1) were SCLC or did not have a primary diagnosis of lung cancer; 2) had not detailed clinical data; 3) had clinical evidence of active infection or inflammation; 4) had hematological disease 5) had a pulmonary embolism, acute myocardial infarction, or cerebrovascular disease within one month 6) active bleeding 7) blood transfusion within the last three months 8) steroid treatment. After inclusion and exclusion criteria, 685 cases were found appropriate for analysis. The initial treatment modalities included operation, chemotherapy, chemoradiotherapy, radiotherapy and best supportive care. This study was approved by the ethics committee of the University of Suleyman Demirel. The written consent was obtained from patients.

Laboratory Data Collection

The data included laboratory information including neutrophil, lymphocyte, platelet counts, hemoglobin level and biochemical parameters such as serum albümin, calcium level, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and CRP. The IPI was calculated by the following formula: CRP × NLR / serum albumin. The cut-off value for each biological baseline parameter was defined as follows: anemia; a hemoglobin level of less than 10 g/dL, thrombocytosis; a platelet count over 450.000/μL, hypoalbuminemia; a serum albumin level of less than 3.0 g/dL, alkaline phosphatase level and lactate dehydrogenase level; above normal level, according to standard laboratory norms, and serum calcium level; hypercalcemia 10.5 gr/dL

Statistical Analysis

A Kaplan-Meier analysis with log-rank test was performed to determine cumulative survival curves. Univariate and multivariate analyses for survival difference were performed using the Cox proportional hazards model and were expressed as hazard ratios (HRs) and 95 % CIs. Overall survival (OS) was calculated

from the diagnosis of the patient to either the date of death from any cause or the date of the last follow-up. Progressionfree survival (PFS) was calculated as the interval between the beginning of time diagnosis and the progression of the disease, recurrence, or death from any cause. Categorical variables were presented as the number of patients and percentages and were compared using Chi-square or Fisher's exact test with odds ratio (OR) and corresponding 95 % confidence interval (CI). Receiver Operating Charateric (ROC) curve analysis was used to determine the cut-off value for NLR, CRP, ESR, Positron emission tomography/ standardized uptake values (PET/SUV) and IPI (respectively; 2.5, 14, 78, 19 and 15). Statistical analyses were performed using SPSS 22.0 software (SPSS Inc. Chicago, IL). All statistical assessments were two-sided and a p-value of 0.05 was considered statistically significant.

Results

Patient Characteristics

Our study included a total of 685 all stage patients with NSCLC including 624 males and 61 females. The median age was 63 years (range: 30 to 88 years). A total of 501 (73.1%) patients had KPS of ≥ 80. For cancer stage, 141 (20.6 %) patients were initially diagnosed as stage 1-2 and 544 (79.4%) as stage 3-4. Association between clinicopathological variables and IPI. The median value of IPI was 21.3 (range, 0.13–2539.6). Using the ROC curve analysis, we found that the optimal cut-off points of IPI for the stratification of OS in NSCLC was determined to be 15. Based on this cutoff value, 334 (48.8 %) patients were categorized as IPI-high group while the remaining 351 (51.2 %) patients as IPI-low group. Clinical and laboratory factors according to IPI groups were presented in Table 1. Age, gender and hystology subtypes were similar between the two groups. However, high IPI was significantly associated with older patients (≥65 years old, P:0.042), high tumor size (T3-4 and ≥4 cm, respectively, P<0.001, P<0.001), high lymph node involvement (N2-3, P<0.001), the presence of distant metastases, (P<0.001), advanced stage (Stage III-IV; P<0.001) and poor performance status (KPS<80, P<0.001).

Survival and Prognostic Factors

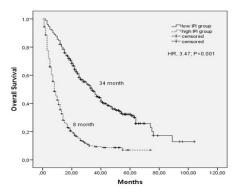At the date of last follow-up, 497 (72.6%) patients had died. Median OS was 17 months (95% CI; 14.73–19.26)

Figure 1. Overall Survival Curves Comparing Patients with NSCLC with a High IPI vs Low IPI

Table 1. Baseline Characteristics Stratified by Pretreatment IPI Level

Characteristics	N(%)	IPI-low,N(%)	IPI-high,N(%)	OR(95%CI)	P
Tumor size					
cT3-4	366 (53.4)	153 (41.8)	213 (58.2)	2.3 (1.7-3.1)	<0.001
cT1-2	319 (46.6)	198 (62.1)	121 (37.9)	1 (Referent)	
Tumor size (as categorical data)*					
≥40 mm	473 (69.1)	210 (44.4)	263 (55.6)	2.5 (1.8-3.5)	<0.001
<40 mm	212 (30.9)	141 (66.5)	71 (33.5)	1 (Referent)	
Lymph nodes					
cN2-3	433 (63.2)	192 (44.3)	241 (55.7)	2.1 (1.6-2.9)	<0.001
cN0-1	252 (36.8)	159 (63.1)	93 (36.9)	1 (Referent)	
Stage					
III-IV	544 (79.4)	246 (45.2)	298 (54.8)	3.6 (2.3-5.3)	<0.001
I-II	141 (20.6)	105 (74.5)	36 (25.5)	1 (Referent)	
Distant metastasis					
Yes	300 (43.8)	107 (35.7)	193 (48.8)	3.1 (2.3-4.3)	<0.001
No	385 (56.2)	244 (63.4)	141 (36.6)	1 (Referent)	
KPS					
<80	184 (26.9)	58 (31.5)	126 (68.5)	3.1 (2.1-4.4)	<0.001
≥80	501 (73.1)	293 (58.5)	208 (41.5)	1 (Referent)	

*NCCN, Guidelines Version 4.2016 Non-Small Cell Lung Cancer, KPS, Karnofsky performance status

and median PFS was 9 months (95% CI; 7.92–10.07). In univariate analyses of survival, low IPI was significantly associated with longer OS compared with high IPI group (median OS in high vs low IPI group, 8.0 vs 34.0 months; HR, 3.47; 95 % CI, 2.88–4.19; p<0.001) (Figure 1). PFS values of the patients who have high IPI vs low IPI were determined 6 months (95% CI:5.3-6.6) and 14 months (95% CI: 12.1-15.8), respectively (HR;2.45, P<0.001) (Figure 2).

Additionaly, prognostic factors and IPI were evaluated by univariate analysis (Table 2). According to this analyses, ≥65 years old, stage III-IV, large primary tumor size (≥ 40mm) and T3-4, regional lymph node (N3-4), distant metastasis, contrlateral lung metastasis, bone metastasis, liver metastasis, brain metastasis, malign pleural effusion, surrenal metastasis, poor performance status (KPS <80), no treatment (chemoterapy, radiotherapy and chemoradiotherapy), high NLR (≥2.5), high LDH level (>230 IU), high calcium level (>10.5 g/dl), low hemoglobin level (<10.5 g/dl) , high CRP level (≥14), high ESR level (≥78) and high IPI (≥15) were also significantly associated with OS. However, no significant

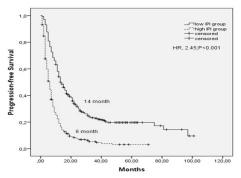difference in OS was noted regarding gender (P=0.088), histology (P=0.944), PET/SUV (P=0.102), hemoglobin level (P=0.336), platalet count (P=0.219).

All significant prognostic factors and IPI tested via multivariate analysis were evaluated using Cox's proportional hazards model. In multivariate analyses, IPI was an independent prognostic factor in NSCLC. Patients with high IPI had increases in the risk of death compared with those with low IPI (HR, 2.35; 95 % CI, 1.79–3.86; p<0.001). Poor PS, extensive disease, high NLR, low serum albümin and abnormally elevated LDH also independently predicted worse OS in NSCLC. All the multivariate survival analyses are presented in Table 2.

In order to investigate the consistency of IPI as a prognostic factor in NSCLC, we also did subgroup analyses according to baseline characteristics. Low IPI predicted favorable OS both in subgroups and all patients (Figure 3).

Figure 2. Progression-Free Survival Curves Comparing Patients with NSCLC with a High IPI vs Low IPI
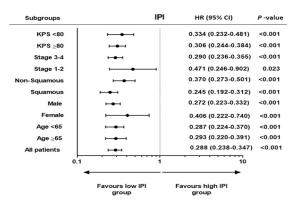

Figure 3. Forest Plot for Subgroup Analysis of Overall Survival. Survival is for low IPI vs high IPI. Data are derived from Cox's analysis without covariates. HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; IPI, inflammatory prognostic index

Table 2. Results of Univariate and Multivariate Cox's Proportional Hazard Models Regarding OS

Characteristics	Univariate Analysis		Multivariate Analysis	
	OS HR (95%CI)	P value	OS HR (95%CI)	P value
Age	1.3 (1.1-1.6)	0.001	0.9 (0.7-1.2)	0.722
(≥65 vs. <65)				
Stage	5.6 (4.1-7.7)	<0.001	3.4 (2.1-5.4)	<0.001
(III-IV vs. I-II)				
Primary tumor size (≥40 mm vs <40 mm)	2.3 (1.9-2.8)	<0.001	2.3 (1.7-3.1)	<0.001
Primary tumor	1.9 (1.5-2.2)	<0.001	1.3 (1.1-1.7)	0.038
(T3-4 vs. T1-2)				
Regional lymph nodes	2.6 (2.1-3.2)	<0.001	1.3 (0.9-1.8)	0.959
(N2-3 vs. N0-1)				
Distant metastasis	3.7 (3.0-4.4)	<0.001	1.9 (1.4-2.6)	<0.001
(Yes vs. No)				
Malign pleural effusion	1.6 (1.1-2.3)	0.019	0.8 (0.5-1.4)	0.422
(Yes vs. No)				
Contralateral lung (Yes vs. No)	2.1 (1.7-2.7)	<0.001	1.3 (0.9-1.9)	0.151
Bone metastasis	2.9 (2.3-3.6)	<0.001	1.2 (0.9-1.8)	0.202
(Yes vs. No)				
Brain metastasis	2.5 (1.9-3.3)	<0.001	1.0 (0.6-1.7)	0.813
(Yes vs. No)				
Liver metastasis	3.1 (2.3-4.2)	<0.001	1.2 (0.8-1.9)	0.334
(Yes vs. No)				
Surrenal metastasis	2.3 (1.8-3.0)	<0.001	0.68 (0.5-1.0)	0.052
(Yes vs. No)				
KPS	4.1 (3.4-5.03)	<0.001	3.6 (2.7-4.8)	<0.001
(<80 vs. ≥80)				
Chemoterapy	1.9 (1.5-2.2)	<0.001	1.2 (1.0-2.1)	0.038
(No vs. Yes)				
Radiotherapy	1.97 (1.56-2.49)	<0.001	0.8 (0.6-1.2)	0.305
(No vs. Yes)				
Chemoradiotherapy	1.96 (1.55-2.50)	<0.001	0.8 (0.5-1.2)	0.288
(No vs. Yes)				
NLR	1.7 (1.4-2.1)	<0.001	1.7 (1.2-2.0)	0.004
(≥2.5 vs. <2.5)				
LDH	1.7 (1.4-2.1)	<0.001	1.3 (1.0-1.7)	0.02
(high vs. normal)				
Calcium	2.7 (2.0-3.6)	<0.001	1.4 (0.9-2.1)	0.094
(high vs low)				
Albumin	2.0 (1.5-2.6)	<0.001	1.6 (1.1-2.3)	0.007
(low vs. high)				
CRP	2.3 (1.8-3.0)	<0.001	1.3 (0.9-1.9)	0.227
(≥14 vs <14)				
ESR	2.1 (1.6-2.7)	<0.001	1.3 (1.0-1.8)	0.058
(≥78 vs. <78)				
IPI	3.5 (2.9-4.2)	<0.001	2.3 (1.8-3.9)	<0.001
(≥15 vs. <15)				

NLR, neutrophil/lymphocyte ratio, LDH; lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein ; ESR, erythrocyte sedimentation rate; IPI, inflammatory prognostic index

Discussion

In this study, we developed a practical index based on laboratory parameters and showed its predictive effect on the survival of early and advanced NSCLC patients. We investigated clinical, hematological, and biochemical

factors. An IPI based on laboratory parameters that was statistically significant in Cox regression analysis (NLR, CRP and Albumin) may be used as a predictor for both OS and PFS. Morever, a multivariate analysis showed that the mortality risks in patients with a high IPI (≥15) increased by 2.3 times.

Various studies have attempted to define the prognostic significance of a range of clinicopathologic factors (Albain et al., 1991; Macchiarini et al., 1993; Ichinose et al., 1995; Mo et al., 2015). The factors that have associated with poor prognosis is large tumor size, nonsquamous histology, metastases to multiple lymph nodes within a TNM-defined nodal station, poor performance status. NSCLC is a heterogeneous disease because of the extreme differences of its prognosis. The differences between the tumor biology and behavior may play a significant role in this heterogeneity. Due to these differences, researchers developed survival indexes by analayzing clinical and laboratory factors for predicting the prognoses of NSCLC patients. In particular the relation between inflammation and prognosis in patients with NSCLC has extensively been studied. Because inflammation is a critical component of tumour progression (Coussens and Werb, 2002). First views on this topic, which was suggested in 1863 by Virchow. He said the origin of cancer that develops from chronic inflammation areas (Balkwill and Mantovani, 2001). From past to today, the causal association between inflammation and cancer is more largely accepted.

CRP is a better indicator of inflammation than the erythrocyte sedimentation rate. It is more sensitive and responds more quickly to changes in the clinical situation (Harrison, 2015). However, both of these inflammatory parameters have been shown to be prognostic in NSCLC (Jing et al., 2015; Engan and Hannisdal, 1990). Albumin is a negative acute-phase protein because its level reduces during injury and sepsis (Sonoda et al., 2015). Furthermore, decreases albumin is not only associated with inflammation closely, but also a negative prognostic factor in patients with NSCLC. In advanced NSCLC, decreased serum albumin level was defined as an index of worse response and survival benefit in patients treated with cisplatin-containing chemotherapy (Moshage et al., 1995; McMillan et al., 2001; Espinosa et al., 1995). Alteration in peripheral blood cells, such as neutrophilia, lymphopenia and thrombocytosis, have been described as responses to systemic inflammation (O'Mahony et al., 1994; Zahorec, 2001). NLR was presented as a chip potential inflammatory marker that has prognostic and predictive values in systemic inflammatory diseases and cancer (Azab et al., 2013; Dirican et al., 2014; Celikbilek et al., 2013). There are many studies showing the significance of NLR as an inflammation marker. Studies showed at the present time that high NLR is a predictive factor of poor prognosis for NSCLC patients (Gu et al., 2015). Researchers have recently published new inflammation-based prognostic scores that was used for predicting the individual prognoses of NSCLC patients. One of them, Jafri et al. have reported inflammatory index called advanced lung cancer inflammation index (ALI) which based on body mass index, serum albumin and NLR (He

et al., 2015). Low ALI at diagnosis time has been reported to be a risk factor for overall survival in advanced NSCLC. They identified cancer cachexia index (CXI) in next article (Jafri et al., 2015). CXI is an improvement on ALI as CXI incorporates skeletal muscle index that is a hallmark of cancer cachexia. Also Glasgow prognostic score which defined as the combination of CRP and albumin is shown the prognostic value for NSCLC (Tomita et al., 2014). The most recent studies on inflammation index in NSCLC have been published by Sun et al. (Sun et al., 2015). They suggested that pretreatment albumin and neutrophil combined prognostic grade could propose an improved prognostic ability in NSCLC patients.

In this study, we firstly developed the prognostic value of the combination of NLR, CRP and albumin in NSCLC patients. IPI is defined by the combination of these three parameters. We further proved that advanced stage, poor KPS, high tumor size, no chemoterapy received and abnormally increased LDH were significantly related to lower OS. More importantly, we established the prognostic value of IPI in NSCLC. In univariate survival analysis, we found that high IPI (≥15) was an indicator of poor OS, achieving a 3.47 times increase in the mortality risk (P<0.001). We also developed the relationship between clinicopathological variables and IPI for excluding potential bias. High IPI was significantly related to with older patients, advanced cancer disease, large tumor size, lymph node metastasis, distant metastasis and poor KPS. Therefore, worse OS in high IPI group might be explained by selection bias because low IPI group included more early stage patients who had better survival than advanced stage. However, our results demonstrate that IPI was an independent prognostic determinant regardless of stage. IPI was shown as a prognostic factor through multivariate analysis including other prognostic factors detected according to univariate analysis. Additionally, subgroup analysis according to stage demonstrated that OS in high IPI group was significantly shorter than that in low IPI group both in stage III and stage III-IV patients. Further we found that high IPI significantly predicts poor OS in all patients subgroups. For the above explained reasons, we think that IPI may be a new and independent prognostic factor for OS in NSCLC patients.

However, IPI may be a non-specific marker for cancer because in other non-cancer situation may be affected. But ın the present study, we excluded such patients and clearly showed that IPI is an independent prognostic determinant in NSCLC. Several limitations remain in this study. First, all the data were retrospectively collected; so, clinical and survival comparison might be influenced by selection bias because of its retrospective nature. Second, our study included a heterogeneous group, there were no restrictions according to clinical parameters such as age, treatment, metastases sites, stage. Third, we could not analyze the correlation of mutation analysis and targeted therapies such as crizotinib and erlotinib with IPI scores. Finally, IPI' alteration did not evaluate in this study.

In conclusion, we have developed an inexpensive test, reproducible and easy to determine, and independent prognostic index for NSCLC patients. It can be easily incorporated into routine use as a prognostic factor. The

prognostic value of this inflammation-based prognostic index needs to be verified in the further validation studies.

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