RESEARCH ARTICLE

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The Inflammatory Prognostic Index Predicts Cancer-Specific Outcomes of Patients with Resected Non-Small Cell Lung Cancer

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Abstract

Background: Previous study developed a new inflammatory prognostic index (IPI) and found the prognostic value of IPI for all stage non-small cell lung cancer (NSCLC). To the best of our knowledge, however, no studies regarding IPI in patients with resected NSCLC are available. **Methods:** Three hundred forty-one NSCLC patients who underwent surgery at our institution were included. The IPI was calculated as C-reactive protein × neutrophil-to-lymphocyte ratio (NLR)/serum albumin. The optimal cut-off value was calculated by the Cutoff Finder. Univariate and multivariate analyses were calculated by the Cox proportional hazards regression model. **Results:** The optimal cut-off value was 5.237 for IPI. The IPI was associated with age, gender, smoking status, histology, pT status and serum CYFRA21-1 level, but not pStage, pN status and serum carcinoembryonic antigen level. The 5-year cancer-specific survival of patients with low IPI was significantly better than that with high IPI (84.8% vs. 57.9%, $p<0.001$). Furthermore, low IPI was significantly associated with favorable cancer-specific survival in univariate (HR =0.326, 95% CI =0.212-0.494; $p<0.001$) and multivariate (HR =0.438, 95% CI =0.276-0.690; $p=0.001$) analyses. **Conclusion:** This is the first study to demonstrate that IPI might serve as an efficient prognostic indicator in resected NSCLC.

Keywords: Inflammatory prognostic index- non-small cell lung cancer- surgery- cancer-specific survival

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Introduction

Primary lung cancer is the leading cause of cancer-related death worldwide (Jemal et al., 2011). Most lung cancer cases (85%) are categorized as non-small cell lung cancer (NSCLC) (Jemal et al., 2011).

It has been well accepted that inflammatory cells are an essential component of the tumor microenvironment, the inflammatory response serve as a crucial role in cancer development and progression and may be associated with systemic inflammation (Mantovani et al., 2008). Emerging evidence suggests that the inflammatory markers have significant correlations with the poor prognosis in NSCLC (Jing et al., 2015; Jin et al., 2017; Gu et al., 2015; Qiang et al., 2016; Okada et al., 2017). One of the most known markers of systemic inflammation is serum C-reactive protein (CRP) level. A meta-analysis clarified that high CRP level is relevant to poorer survival of NSCLC patients and might be used as a prognostic biomarker for NSCLC (Jing et al., 2015). Furthermore, the combination of some parameters, including Glasgow prognostic score (GPS), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and prognostic nutritional index (PNI), has been used in the prognosis of NSCLC (Jin et al., 2017; Gu et al., 2015; Qiang et al., 2016; Okada et al., 2017). These biomarkers may be used as practical predictors in the daily clinical work.

Recently, a new inflammatory prognostic index (IPI), based on CRP, NLR and serum albumin was introduced as a novel and promising prognostic marker in all stage NSCLC patients (Dirican et al., 2016). They concluded that IPI may be an inexpensive, easily accessible and independent prognostic index for NSCLC patients (Dirican et al., 2016). However, 79.4% of their patients were stage III-IV disease. To our knowledge, there are no previous studies that evaluated the significance of IPI for resected NSCLC. Therefore, in the present study, we examined the prognostic significance of IPI in patients with resected NSCLC.

Materials and Methods

Patients and Methods

This retrospective study examined the records of a sequential series of 381 patients with NSCLC between January 2008 and December 2012 in our center. There

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were 173 men and 168 women (median age: 69 years old). The inclusion criteria were as following: histologically confirmed NSCLC and complete clinical, laboratory, imaging and follow-up data. The exclusion criteria included: preoperative chemotherapy/radiotherapy or died perioperative period, clinical evidence of infection or other bone marrow, hematological or autoimmune disease. This retrospective study was approved by Medical Ethics Committee of our hospital. Complete blood count and routine biochemistry test, including serum CRP, serum albumin, serum carcinoembryonic antigen (CEA) and serum cytokeratin 19 fragments (CYFRA21-1), of each patient was applied 1 week before surgery. All patients in this study were staged according to the 8th edition Cancer Staging (Goldstraw et al., 2016). The IPI was calculated as CRP (mg/L) × NLR/serum albumin (g/L) (Dirican et al., 2016). The optimal cut-off value of IPI for overall cancer-specific survival was determined by Cutoff Finder (http://molpath.charite.de/cutoff) (Budczies et al., 2012).

Association between categorical variables was assessed using the Fisher's exact test. Cancer-specific survival curves were plotted using the Kaplan–Meier method, with comparisons between groups performed using the log-rank test. Cox regression models were used to assess the relationships between the IPI and cancer-specific survival. After univariate analysis, a multivariate analysis was carried out by Cox regression model. Estimated hazard ratios, their 95% confidence intervals (95% CI), and p values were calculated from the Cox proportional hazard regression models. Statistical analyses were performed using JMP (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant when $p < 0.05$.

Results

Analysis using the Cutoff Finder showed the recommended cutoff values of preoperative IPI for evaluating cancer-specific survival was 5.237. There were 213 (62.46%) patients with low IPI group and 128 (37.53%) patients with high IPI group. The relationships between IPI and clinical characteristics were shown in Table 1. In the present series, IPI was significantly associated with age (p=0.008), gender (p<0.001), smoking status (p<0.001), histology (p<0.001), pT status (p=0.049) and CYFRA21-1 (p=0.001), but not pStage (p=0.085), pN status (p=0.409) and serum CEA level (p=0.93).

The 5-year overall cancer-specific survival was 74.9% in our study. As shown in Figure 1, patients with high IPI had a significantly poor 5-year cancer-specific survival compared to low IPI (57.9% vs. 84.8%, p<0.001).

By univariate analysis, gender, smoking status, histology, pT status, pN status, serum CEA level, serum CYFRA21-1 level, serum CRP level and IPI were significant association with the 5-year cancer-specific survival. All 8 clinicopathological characteristics were further investigated in multivariate analysis. As shown in Table 3, gender (p=0.009), histology (adenocarcinoma vs. squamous cell carcinoma: p<0.001, adenocarcinoma vs. others: p=0.001), pN status (p=0.001), serum CEA level (p=0.002) and IPI (p<0.001) were independent factors in predicting overall postoperative cancer specific survival, while smoking status, pT status and serum CYFRA21-1 level were not.

Table 1. Clinical Characteristics of Patients based on the IPI

	IPI		P-Value
	Low	High	
Age			
<65	77	29	0.008
≥65	136	99	
Gender			
Male	85	88	<0.001
Female	128	40	
Smoking status			
Never	122	36	<0.001
Current/former	91	92	
Histology			
AD	186	82	<0.001
SCC	13	30	
Others	14	16	
pStage			
I	172	93	0.085
II-III	41	35	
pT status			
pT1	155	80	0.049
pT2-3	58	48	
pN status			
pN0	185	107	0.409
pN1-2	28	21	
Serum CEA			
Normal	159	95	0.93
High	54	33	
CYFRA21-1			
Normal	188	95	0.001
High	25	33	

IPI, inflammatory prognostic index; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragments; AD, adenocarcinoma; SCC, squamous cell carcinoma.

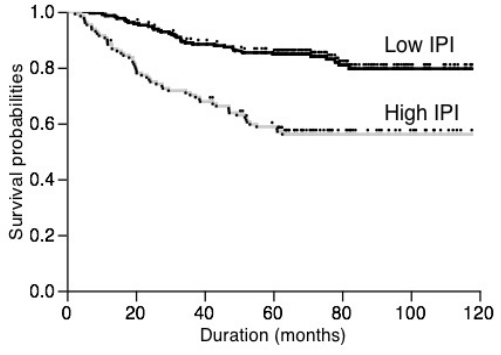

Figure 1. Overall Postoperative Cancer-Specific Survival of Patients based on Inflammatory Prognostic Index (IPI).

Table 2. Univariate Analysis

	Favorable	Unfavorable	Hazard ratio	P-Value	95% confidence interval	
					Lower	Upper
Age	<65	≥65	0.755	0.235	0.461	1.193
Gender	Female	Male	0.329	<0.001	0.204	0.514
Smoking status	Never	Current/former	0.349	<0.001	0.215	0.549
Histology	AD	SCC	0.26	<.0001	0.162	0.43
	AD	Others	0.234	<.0001	0.135	0.432
	SCC	Others	0.9	0.751	0.477	1.755
pT status	pT1	pT2-3	0.45	<0.001	0.298	0.683
pN status	pN0	pN1-2	0.33	<0.001	0.211	0.534
CEA	Normal	High	0.382	<0.001	0.252	0.586
CYFRA21-1	Normal	High	0.353	<0.001	0.229	0.556
IPI	Low	High	0.326	<0.001	0.212	0.494

IPI, inflammatory prognostic index; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragments; CI, confidence interval; AD, adenocarcinoma; SCC, squamous cell carcinoma.

Table 3. Multivariate Analysis

	Favorable	Unfavorable	Hazard ratio	p Value	95% confidence interval	
					Lower	Upper
Gender	Female	Male	0.422	0.009	0.214	0.81
Smoking status	Never	Current/former	0.781	0.489	0.396	1.584
Histology	AD	SCC	0.42	<0.001	0.263	0.676
	AD	Others	0.306	0.001	0.169	0.584
	SCC	Others	0.607	0.159	0.31	1.223
pT status	pT1	pT2-3	0.967	0.893	0.6	1.58
pN status	pN0	pN1-2	0.365	0.001	0.214	0.635
CEA	Normal	High	0.473	0.002	0.302	0.748
CYFRA21-1	Normal	High	0.783	0.357	0.473	1.326
IPI	Low	High	0.438	<0.001	0.276	0.69

IPI, inflammatory prognostic index; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragments; CI, confidence interval; AD, adenocarcinoma; SCC, squamous cell carcinoma.

Discussion

To our knowledge, this was the first report investigating the prognostic value of IPI in resected patients with NSCLC. In this study, we revealed that IPI was an independent significant predictive factor for resected NSCLC.

The systemic inflammation response of the host is one of the representative biomarkers of host-related factors that predict the prognosis of cancer (Scott et al., 2002). A significant positive correlation between serum CRP level and progression of NSCLC has been reported (Jing et al., 2015). High serum CRP level has also been associated with increased weight loss, reduced performance status, increased fatigue and decreased survival (Jing et al., 2015). Based on these findings, high serum CRP level may predict poor survival.

Neutrophils influences tumor initiation and progression in the tumor microenvironment and impede the activity of lymphocytes and other immune cells, whereas lymphocytes suppress tumor growth and invasion through their cytolytic activity, and was associated with a survival benefit (Gooden et al., 2011). A high NLR is detected when the absolute neutrophil count is high and the absolute lymphocyte count is low. Therefore, high neutrophil may aid in the development and progression of tumor and a relative lymphocytopaenia may exhibit a poorer lymphocyte mediated immune response to tumor.

Low serum albumin could represent the compromised nutritional status of the host, as well as the response of systemic inflammation (Sun et al., 2015; Espinosa et al., 1995). Previous studies demonstrated that hypoalbuminemia was associated with poor prognosis and decreased survival in NSCLC (Sun et al., 2015; Espinosa et al., 1995).

Taken together, the combination of CRP, NLR and serum albumin may serve as a more effective scoring system to predict prognosis of NSCLC patients. Thus, a high IPI, due to high levels of serum CRP and neutrophils while low level of lymphocytes and serum albumin, suggests a stronger inflammatory and a weaker immune response in patients. It may be associated with invasion and metastasis of cancer cells and hence lead to poor survival.

In the present series, IPI was significantly associated with age, gender, smoking status, histology, pT status and CYFRA21-1, but not pStage, pN status and serum CEA level. This indicated that IPI does not always correlate with more advance and aggressive disease phenotypes. Furthermore, the results of multivariable analysis showed that IPI is an independent prognostic factor.

IPI was based on four factors (CRP, neutrophil, lymphocyte and albumin) (Dirican et al., 2016), while GPS, NLR, PLR and PNI, were based on two factors (Jin et al., 2017; Gu et al., 2015; Qiang et al., 2016; Okada et al., 2017). IPI should be a more objective marker that reflects the balance between host inflammatory and immune response status than all the other systemic inflammation scores.

IPI is simple, inexpensive and it doesn't require extra equipment. Thus, IPI should be taken into consideration in the therapeutic program for resected NSCLC. It would be very useful to carry extensive study in several countries for better conclusions and recommendations.

Our study had several limitations. It was a single-center, retrospective study with a relatively small sample size. A new cutoff value might be got when we examine it in large number of cases. Thus, conclusions from the present study may have a bias, indicating that prospective cohort and multicenter studies to find a proper cutoff value are needed.

In conclusions, to the best of our knowledge, this is the first report to demonstrate the prognostic role of IPI in patients with resected NSCLC.

Conflict of interest

The authors have declared that no conflict of interest exists.

References

Budczies J, Klauschen F, Sinn BV, et al (2012). Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. *PLoS One*, **7**, e51862.

Dirican N, Dirican A, Anar C, et al (2016). 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. *Asian Pac J Cancer Prev*, **17**, 5101-6.

Espinosa E, Feliu J, Zamora P, et al (1995). Serum albumin and other prognostic factors related to response and survival in patients with advanced non-small cell lung cancer. *Lung Cancer*, **12**, 67-76.

Goldstraw P, Chansky K, Crowley J, et al (2016). The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*, **11**, 39-51.

Gooden MJ, de Bock GH, Leffers N, et al (2011). The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. *Br J Cancer*, **105**, 93-103.

Gu XB, Tian T, Tian XJ, et al (2015). Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis. *Sci Rep*, **5**, 12493.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Jin J, Hu K, Zhou Y, et al (2017). Clinical utility of the modified Glasgow prognostic score in lung cancer: A meta-analysis. *PLoS One*, **12**, e0184412.

Jing X, Huang C, Zhou H, et al (2015). Association between serum C-reactive protein value and prognosis of patients with non-small cell lung cancer: a meta-analysis. *Int J Clin Exp Med*, **8**, 10633-9.

Mantovani A, Allavena P, Sica A, et al (2008). Cancer-related inflammation. *Nature*, **454**, 436-44.

Okada S, Shimada J, Kato D, et al (2017). Clinical significance of prognostic nutritional index after surgical treatment in lung cancer. *Ann Thorac Surg*, **104**, 296-302.

Qiang G, Liang C, Xiao F, et al (2016). Prognostic significance of platelet-to-lymphocyte ratio in non-small-cell lung cancer: a meta-analysis. *Onco Targets Ther*, **9**, 869-76.

Scott HR, McMillan DC, Forrest LM, et al (2002). The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. *Br J Cancer*, **87**, 264-7.

Sun H, Hu P, Shen H, et al (2015). Albumin and neutrophil combined prognostic grade as a new prognostic factor in non-small cell lung cancer: results from a large consecutive cohort. *PLoS One*, **10**, e0144663.