Preoperative Serum C-reactive Protein Level in Non-small Cell Lung Cancer

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Abstract. *We evaluated the significance of the preoperative serum C-reactive protein (CRP) level as a prognostic indicator in patients with non-small cell lung cancer (NSCLC). Patients and Methods: Two hundred and three patients who had undergone a curative resection of NSCLC were retrospectively reviewed. Results: The proportion of the tumor size over 3 cm per patient in the CRP-positive group (≥0.5 mg/dL: n=38) was significantly higher than that in the CRP-negative group (<0.5 mg/dL: n=165). The proportion of the adenocarcinoma in CRP-positive group was significantly lower than that in CRP-negative group. The overall and disease specific survival rates in the CRP-positive group were significantly lower than the rates in the CRP-negative group. Based on a multivariate analysis, the preoperative serum CRP level was selected as one of the unfavorable indicators regarding survival. Conclusion: The preoperative serum CRP level is an independent and significant indicator predictive of a poor prognosis in patients with NSCLC.*

C-reactive protein (CRP) is an acute-phase reactant. The preoperative serum elevation of CRP has been identified to be a significant prognostic factor in patients with colorectal (1, 2), esophageal (3, 4), hepatic (5), and pancreas cancer (6). The plasma CRP level has been shown to be associated with non-small cell carcinoma (NSCLC) (7) and the prognosis of advanced NSCLC (8). However, no previous study has ever described a relationship between the preoperative peripheral CRP level and the prognosis in NSCLC patients who underwent a curative operation. The aim of this study was to investigate the significance of CRP in the long-term prognosis in a NSCLC patient population who had all undergone a curative operation.

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Patients and Methods

Two hundred and three patients who had undergone a curative resection of NSCLC between January 1998 and December 2003 were enrolled in this study. Curative operations were defined those of the patients with no residual macroscopic disease after surgery. Blood samples were obtained prior to the surgery. The serum levels of CRP were measured by a latex photometric immunoassay (Mitsubishi Kagaku Iatron, Tokyo, Japan). Patients with serum CRP levels <0.5 mg/dL were assigned to the CRP-negative group, whereas patients with serum CRP levels ≥0.5 mg/dL were assigned to the CRP-positive group according to the manufacturer's instructions. We also measured the serum levels of lactate dehydrogenase (LDH) (normal limits, 119-229 U/L) and white blood cell (WBC) count (5000-9000/mm^3).

The Mann-Whitney *U*-test was used for the statistical analysis. The categorical data were compared using the χ^2 test. Survival was evaluated by the Kaplan-Meier method, and differences among the survival curves were tested using the log-rank test. Multivariate analyses according to the Cox's proportional hazards model was used to assess the overall and disease-specific survivals as well as the influence of the clinical parameters. Statistical calculations were conducted with JMP (SAS Institute Inc. Cary, NC, USA) and values of p less than 0.05 were accepted as significant.

Results

A preoperative elevation of serum CRP value was recognized in 38 (18.7%) patients, whereas no such elevation was recognized in 165 (81.3%). The clinicopathological characteristics are shown in Table I. No significant difference was observed regarding age or gender between the two groups ($p=0.0634$ and $p=0.7247$, respectively). Although no significant difference was observed regarding the preoperative LDH level between the two groups ($p=0.7454$), the mean preoperative WBC count in CRP positive group was significantly higher than that in the CRP negative group ($p<0.0001$). The proportion of patients with a tumor size of over 3 cm in the CRP-positive group

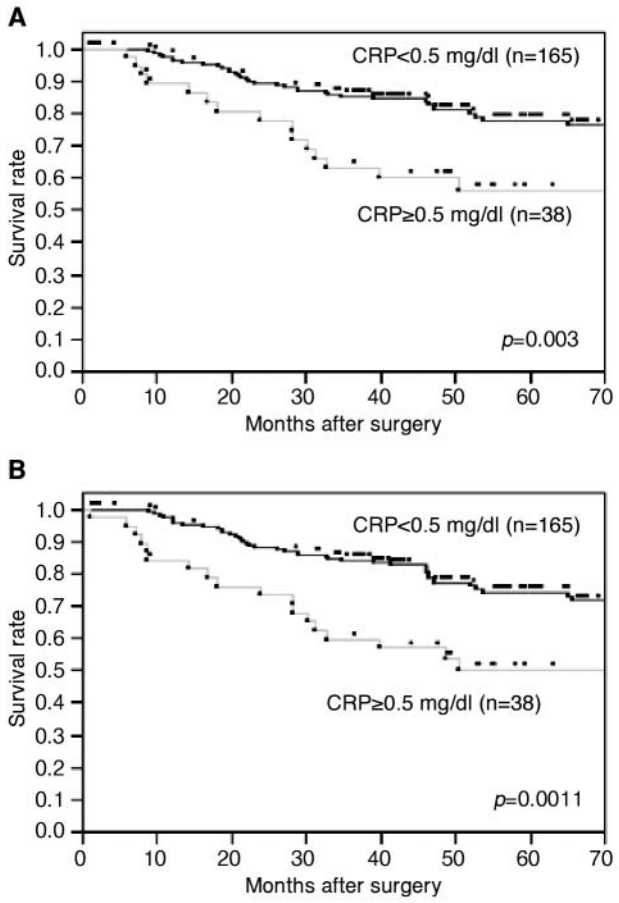

Figure 1. *Survival curves for patients with NSCLC (Stage I ~ IIIA) after a curative resection. High CRP group (n=38) vs. low CRP group (n=165). The p-values were demonstrated using the Log-rank test. A: disease specific survival, B: overall survival.*

(63.2%) was significantly higher than that in the CRP-negative group (35.2%; $p=0.0015$). No significant difference was seen between the proportions of histopathologically detected lymph node metastases between two groups ($p=0.3959$). The proportion of adenocarcinoma in the CRP-positive group (47.4%) was significantly lower than that in the CRP-negative group (75.2%; $p=0.0004$). No significant difference was observed in proportion of the surgical treatment method in the two groups ($p=0.5660$). Forty-one patients received adjuvant chemotherapy, 21 patients had uracil-tegafur for two years and 20 patients had cisplatin based chemotherapy for from two to four cycles. No significant difference was observed in the proportion of adjuvant chemotherapy in the two groups ($p=0.5586$).

The 5-year disease specific survival and overall survival rates in CRP-positive group were 56.2% and 50.2%, respectively; and they were significantly more unfavorable than those in the CRP-negative group, which were 77.6% ($p=0.003$) and 74.2% ($p=0.0011$), respectively (Figure 1).

Table I. *The relationship between the preoperative CRP levels and the clinicopathological characteristics in 203 patients with non-small cell lung cancer.*

Characteristics	CRP<0.5 mg/dl (n=165)	CRP≥0.5 mg/dl (n=38)	*p*
Male/female	103/62	28/10	0.0634
Age, years (range)	70.0 (20-85)	65.9 (41-83)	0.7247
Preoperative LDH (U/L)	224±95	225±84	0.7454
Preoperative WBC (/mm^3)	5709±1325	7516±2967	<0.0001
Tumor size			
≤3 cm	107	14	
>3 cm	58	24	0.0015
pN factor			
pN0	124	29	
pN1	17	6	
pN2	14	3	0.3959
Histology			
adenocarcinoma	125	18	
squamous cell carcinoma	27	18	
large cell carcinoma	8	2	
others	5	0	0.0004
Operational procedure			
lobectomy	152	33	
bilobectomy	11	4	
pneumonectomy	2	1	0.5660
Adjuvant chemotherapy			
no	133	29	
yes	32	9	0.5586

The factors that were considered in the univariate analysis are summarized in Table II. The factors that were significantly associated with a limited survival were gender ($p=0.0102$), tumor size ($p<0.0001$), nodal metastasis ($p<0.0001$), histology ($p=0.0022$), adjuvant chemotherapy ($p=0.0011$), preoperative WBC count ($p=0.0442$) and the preoperative peripheral CRP level (0.0030). The variables factors were entered into the Cox proportional hazards model by a forward stepwise procedure and the results of multivariate analysis are summarized in Table III. A multivariate analysis showed the tumor size (>3 cm), lymph node metastasis (N1-2), and an elevated preoperative serum CRP level to demonstrate a significant difference ($p<0.0016$, $p<0.0001$ and $p=0.0254$, respectively).

Discussion

We herein demonstrated that the preoperative serum CRP level might be an independent and significant prognostic indicator in patients with NSCLC after a curative operation. Both the disease specific survival and the overall survival rates in the CRP-positive group were significantly lower than the rates in the CRP-negative group. To the best of our knowledge, this is the first report to demonstrate the

Table II. *Univariate analysis of prognostic factors.*

Factors	Hazard ratio (95% CI)	*p*-value
Age	0.999 (0.976-1.027)	0.9651
Gender (female *vs.* male)	1.448 (1.088-1.991)	0.0102
Tumor size (≤3 cm *vs.* >3cm)	1.708 (1.323-2.226)	<0.0001
Nodal metastasis (N0 *vs.* N1-2)	2.113 (1.613-2.745)	<0.0001
Histology (adenocarcinoma *vs.* others)	1.509 (1.164-1.946)	0.0022
Adjuvant chemotherapy (no *vs.* yes)	1.642 (1.231-2.156)	0.0011
CRP (<0.5 mg/dl *vs.* ≥0.5mg/dl)	1.552 (1.169-2.022)	0.0030
LDH (≤229U/L *vs.* >229U/L)	1.152 (0.763-1.625)	0.4715
WBC (≤9000/mm^3 *vs.* >9000/mm^3)	1.575 (1.013-2.259)	0.0442

Table III. *Multivariate analysis of the prognostic factors.*

Factors	Hazard ratio (95% CI)	*p*-value
Gender (female *vs.* male)	1.205 (0.888-1.680)	0.2361
Tumor size (≤3 cm *vs.* >3 cm)	1.533 (1.173-2.015)	0.0018
Nodal metastasis (N0 *vs.* N1-2)	2.247 (1.568-3.179)	<0.0001
Histology (adenocarcinoma *vs.* others)	1.100 (0.817-1.474)	0.5262
Adjuvant chemotherapy (no *vs.* yes)	0.954 (0.649-1.385)	0.8077
CRP (<0.5 mg/dl *vs.* ≥0.5 mg/dl)	1.435 (1.048-1.941)	0.0254
WBC (≤9000/mm^3 *vs.* >9000/mm^3)	0.888 (0.538-1.397)	0.6153

significance of the preoperative serum CRP level in the prognosis of patients who have been operated on for NSCLC.

The prognosis value of the CRP levels has been reported for curative operable solid cancer other than those in the lung such as liver (5), esophagus (3, 9) and colon cancers (1, 2, 10). The mechanism by which cancer is accompanied by increased CRP level is well known. CRP liver production is strongly induced by cytokines such as interleukin (IL) 1, TNF, and mostly IL-6. Experimental studies in the NSCLC cell lines and expression studies in lung surgical specimens showed that at least some NSCLC tumors are actually able to produce IL-6 (11, 12) and TNF-α (13).

In contrast, the reason why the CRP levels may be correlated with the prognosis in cancer patients remain to be determined. Jones *et al.* (7) reported the serum CRP level to positively correlate with the maximum pathological tumor size but not the pN stage, which is same as our results (Table I). They also showed the incidence of an incomplete resection was higher in CRP high group, suggesting CRP-positive group might contain latent inoperable patients. One explanation for this hypothesis is that patients with high serum CRP levels might already have a cytological tumor spread that cannot be detected either by routine imaging studies or by pathologic examinations. Another explanation is that circulating NSCLC cells in either the peripheral blood or lymph nodes might play an important role in the early recurrence in patients who have high CRP levels (14). As a target of IL-6 action in the liver, CRP is a marker of IL-6 tumor production. Recent studies have revealed IL-6 to block the apoptosis induced by p53, transforming growth factor β and certain cancer chemotherapeutic compounds (15-17). As a result, the CRP-positive group might have a tumor microenvironment that is suitable for the survival of remnant tumor cells by up-regulating the acute inflammatory cytokine network system. As a result, the preoperative CRP elevation is thus considered to be a poor prognostic factor. Therefore, patients demonstrating a high preoperative CRP level might need adjuvant chemotherapy and/or a close follow-up.

In conclusion, the present study showed a higher preoperative serum CRP level to be an independent factor for a poor prognosis. The serum CRP dosage is a simple, reliable, and reproducible method in which the interpretation is also relatively easy. We therefore propose the preoperative CRP level as a useful adjunct diagnostic modality which can be routinely performed during the screening of patients with NSCLC.

References

1 Nikiteas NI, Tzanakis N, Gazouli M, Rallis G, Daniilidis K, Theodoropoulos G, Kostakis A and Peros G: Serum IL-6, TNFalpha and CRP levels in Greek colorectal cancer patients: prognostic implications. World J Gastroenterol *11*: 1639-1643, 2005.

2 Miki C, Konishi N, Ojima E, Hatada T, Inoue Y and Kusunoki M: C-reactive protein as a prognostic variable that reflects uncontrolled up-regulation of the IL-1-IL-6 network system in colorectal carcinoma. Dig Dis Sci *49*: 970-976, 2004.

3 Gockel I, Dirksen K, Messow CM and Junginger T: Significance of preoperative C-reactive protein as a parameter of the perioperative course and long-term prognosis in squamous cell carcinoma and adenocarcinoma of the oesophagus. World J Gastroenterol *12*: 3746-3750, 2006.

4 Guillem P and Triboulet JP: Elevated serum levels of C-reactive protein are indicative of a poor prognosis in patients with esophageal cancer. Dis Esophagus *18*: 146-150, 2005.

5 Hashimoto K, Ikeda Y, Korenaga D, Tanoue K, Hamatake M, Kawasaki K, Yamaoka T, Iwatani Y, Akazawa K and Takenaka K: The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. Cancer *103*: 1856-1864, 2005.

6 Falconer JS, Fearon KC, Ross JA, Elton R, Wigmore SJ, Garden OJ and Carter DC: Acute-phase protein response and survival duration of patients with pancreatic cancer. Cancer *75*: 2077-2082, 1995.

7 Jones JM, McGonigle NC, McAnespie M, Cran GW and Graham AN: Plasma fibrinogen and serum C-reactive protein are associated with non-small cell lung cancer. Lung Cancer *53*: 97-101, 2006.

8 Tas F, Duranyildiz D, Argon A, Oguz H, Camlica H, Yasasever V and Topuz E: Serum levels of leptin and proinflammatory cytokines in advanced-stage non-small cell lung cancer. Med Oncol *22*: 353-358, 2005.

9 Shimada H, Nabeya Y, Okazumi S, Matsubara H, Shiratori T, Aoki T, Sugaya M, Miyazawa Y, Hayashi H, Miyazaki S and Ochiai T: Elevation of preoperative serum C-reactive protein level is related to poor prognosis in esophageal squamous cell carcinoma. J Surg Oncol *83*: 248-252, 2003.
10 Nozoe T, Matsumata T, Kitamura M and Sugimachi K: Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. Am J Surg *176*: 335-338, 1998.
11 Matsuguchi T, Okamura S, Kawasaki C, Shimoda K, Omori F, Hayashi S, Kimura N and Niho Y: Constitutive production of granulocyte colony-stimulating factor and interleukin-6 by a human lung cancer cell line, KSNY: gene amplification and increased mRNA stability. Eur J Haematol *47*: 128-133, 1991.
12 Katsumata N, Eguchi K, Fukuda M, Yamamoto N, Ohe Y, Oshita F, Tamura T, Shinkai T and Saijo N: Serum levels of cytokines in patients with untreated primary lung cancer. Clin Cancer Res 2: 553-559, 1996.
13 Niiya M, Niiya K, Kiguchi T, Shibakura M, Asaumi N, Shinagawa K, Ishimaru F, Kiura K, Ikeda K, Ueoka H and Tanimoto M: Induction of TNF-alpha, uPA, IL-8 and MCP-1 by doxorubicin in human lung carcinoma cells. Cancer Chemother Pharmacol *52*: 391-398, 2003.
14 Jiao X and Krasna MJ: Clinical significance of micrometastasis in lung and esophageal cancer: a new paradigm in thoracic oncology. Ann Thorac Surg *74*: 278-284, 2002.
15 Jee SH, Shen SC, Chiu HC, Tsai WL and Kuo ML: Overexpression of interleukin-6 in human basal cell carcinoma cell lines increases anti-apoptotic activity and tumorigenic potency. Oncogene *20*: 198-208, 2001.
16 Frassanito MA, Cusmai A, Iodice G and Dammacco F: Autocrine interleukin-6 production and highly malignant multiple myeloma: relation with resistance to drug-induced apoptosis. Blood *97*: 483-489, 2001.
17 Chauhan D, Kharbanda S, Ogata A, Urashima M, Teoh G, Robertson M, Kufe DW and Anderson KC: Interleukin-6 inhibits Fas-induced apoptosis and stress-activated protein kinase activation in multiple myeloma cells. Blood *89*: 227-234, 1997.

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