Original Article

Postoperative Serum C-Reactive Protein Levels in Non-Small Cell Lung Cancer Patients

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Purpose: The significance of the postoperative serum C-reactive protein (CRP) level as a prognosis indicator was evaluated in patients with non-small cell lung cancer (NSCLC).
Patients and Methods: A total of 276 patients who had undergone a curative resection of NSCLC were retrospectively reviewed.
Results: The overall and disease-specific survival rates in the postoperative CRP/high group (≥ 0.5 mg/dL at 30 days postoperation: n = 130) were significantly lower than those in the postoperative CRP/low group (< 0.5 mg/dL at 30 days postoperation: n = 146). However, based on a multivariate analysis, the postoperative CRP level was not among the unfavorable indicators regarding survival. The patients were divided into two groups, namely, the preoperative CRP/low group (n = 231) and the CRP/high group (n = 45). The proportion of the postoperative CRP/low group (60.2%) in the preoperative CRP/low group was significantly lower than that in the preoperative CRP/low group (15.6%; p <0.0001). No significant difference was observed in the disease-specific survival rates in the postoperative CRP/high group and the postoperative CRP/low group in either the preoperative high/group or low/group.
Conclusions: The overall and disease-specific survival rates in the postoperative CRP/high group were significantly lower than that in the postoperative CRP/low group. This difference may be associated with the relationship between the pre- and postoperative CRP levels. (Ann Thorac Cardiovasc Surg 2010; 16: 85–90)

Key words: C-reactive protein, non-small cell lung cancer, inflammatory protein, prognosis

Introduction

C-reactive protein (CRP) is the phenotype acute-phase protein, which can increase up to 1,000-fold after the onset of a stimulus.[1] The preoperative serum elevation of CRP has been identified to be a significant prognostic factor in patients with colorectal,[2,3] esophageal,[4] hepatic[5] and non-small cell lung cancer (NSCLC).[6] CRP is produced mainly by hepatocytes, and its production is regulated by interleukin-6 (IL-6). Several possible mechanisms have been proposed for the relationship between CRP and cancer.[7] Some are that tumor cells themselves cause tissue inflammation and thus increase CRP levels. If so, CRP levels after a curative operation should be decreased to normal range. If the CRP level recovers to normal, the prognoses of patients should be better than that of patients with continued elevation of CRP. The aim of this study was to investigate the significance of postoperative CRP recovery in the long-term prognosis of a NSCLC patient population following curative resection.

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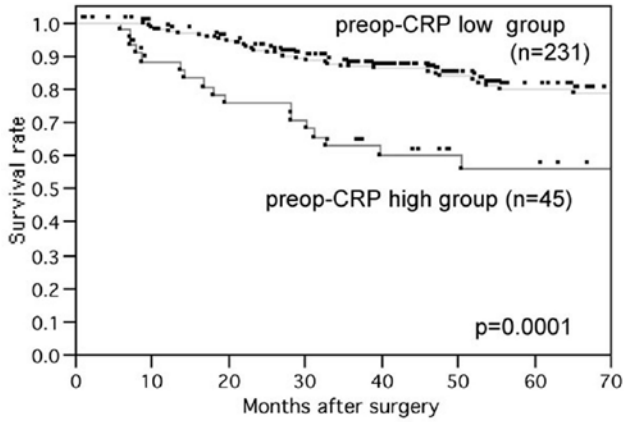

Fig. 1. Disease-specific survival curves for patients with NSCLC (stages I–IIIA) after a curative resection. Preoperative CRP/high group (n = 45) vs. preoperative CRP/low group (n = 231). The p value was determined using the log-rank test.

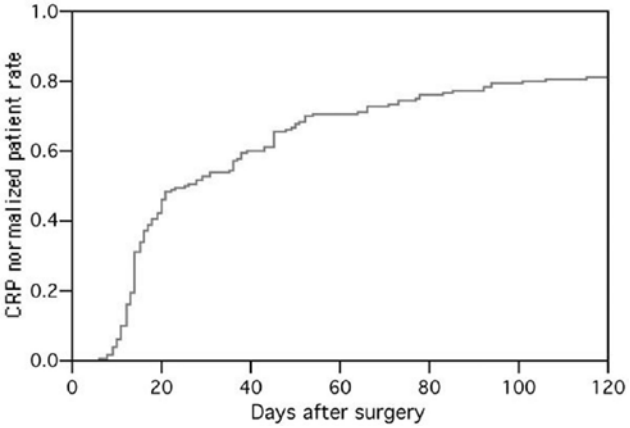

Fig. 2. Rate of CRP normalized patients among patients with NSCLC (stages I–IIIA) after a curative resection.

Patients and Methods

A total of 293 consecutive patients who had undergone a curative resection of NSCLC from January 1998 to December 2005 were enrolled in this study. Curative operations were defined as those in which patients had no residual macroscopic disease after surgery. Blood samples were obtained prior to the surgery and three times a week the first two weeks, two times a week in the third week, once every two weeks for two months, and once three months after the operation. Excluded from this study were 17 patients whose CRP levels could not be assessed after the operation. The serum levels of CRP were measured by a latex photometric immunoassay (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan). Patients with serum CRP levels < 0.5 mg/dL were assigned to the CRP/low group, whereas patients with serum CRP levels ≥ 0.5 mg/dL were assigned to the CRP/high group, according to the manufacturer's instructions. Moreover, the serum levels of lactate dehydrogenase (LDH) (normal limits, 119–229 U/L) and the white blood cell (WBC) count (5,000–9,000/mm^3) were assessed.

The Mann-Whitney U test was used for statistical analysis. The categorical data were compared using the c^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 were used to assess the overall and disease-specific survival as well as the influence of clinical parameters. Statistical calculations were conducted with JMP (SAS Institute Inc., Cary, NC, USA), and values of p less than 0.05 were considered significant.

Results

A preoperative elevation of the serum CRP value was recognized in 45 (16.3%) patients, whereas no such elevation was recognized in 231 (83.7%). The 5-year disease-specific survival and overall survival rates in the preoperative CRP/high group were 56.1% and 49.0%, and they were significantly more unfavorable than those in the preoperative CRP/low group, which were 80.0% (p = 0.0001) and 75.8% (p <0.0001) (Fig. 1).

The postoperative serum CRP was normally elevated after the operation and gradually declined in all patients (data not shown). As shown in Fig. 2, the serum CRP level declined to normal level in 146 of 276 patients (52.9%), whereas no such decline was obtained in 130 (47.1%) at 30 days postoperation. The postoperative CRP/low group was defined as patients whose serum CRP level was normalized within 30 days after the operation. The clinicopathological characteristics are shown in Table 1. Although no significant difference was observed with regard to age between the two groups (p = 0.3347), the female patient ratio in the postoperative CRP/low group was significantly higher than in the postoperative CRP/high group (p <0.0001). And even though no significant difference was observed regarding the mean preoperative LVH level between the two groups (p = 0.0613), the mean preoperative CRP level or preoperative

Table 1. Relationship between the postoperative CRP levels and the clinicopathological characteristics in 276 patients with non-small cell lung cancer

Characteristics	CRP < 0.5 mg/dl (n = 146)	CRP ≥ 0.5 mg/dl (n = 130)	p
Gender (male/female)	73/73	98/33	<0.0001
Age, years (range)	66.5 (37–86)	67.1 (20–85)	0.3347
Preoperative CRP (mg/dl)	0.14 ± 0.25	1.07 ± 2.54	<0.0001
Preoperative LDH (U/L)	201 ± 69	222 ± 9	0.0613
Preoperative WBC (/mm^3)	5,588 ± 1,261	6,222 ± 2,086	0.0094
Tumor size			
≤ 3 cm	102	71	
> 3 cm	44	59	0.0174
T factor			
T1	96	64	
T2	43	54	
T3	7	12	0.0174
N factor			
N0	120	97	
N1	9	17	
N2	17	16	0.1322
Histology			
Adenocarcinoma	120	90	
Squamous cell carcinoma	14	34	
Large cell carcinoma	6	4	
Others	6	2	0.0027
Operational procedure			
Lobectomy	146	120	
Bilobectomy	7	8	
Pneumonectomy	1	2	0.6939
Adjuvant chemotherapy			
No	110	97	
Yes	36	33	0.8893

CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell.

WBC count in the postoperative CRP/high group was significantly higher than that in the postoperative CRP/low group (p <0.0001 and p = 0.0094). The proportion of patients with a tumor size exceeding 3 cm in the postoperative CRP/high group (45.4%) was significantly higher than in the postoperative CRP/low group (30.1%; p = 0.0174). No significant difference was observed in the proportion of histopathologically detected lymph node metastases between the two groups (p = 0.1322). The proportion of adenocarcinoma in the postoperative CRP/high group (69.2%) was significantly lower than in the postoperative CRP/low group (82.2%; p = 0.0027). No significant difference in proportion to the surgical treatment method was observed in the two groups (p = 0.6939). Sixty-nine patients received adjuvant chemotherapy, 43 had uracil-tegafur for 2 years, and 26 had cisplatin-based chemotherapy for two to four cycles. No significant difference was observed in the two groups (p = 0.8893).

The 5-year disease-specific survival and overall survival rates in the postoperative CRP/high group were 68.6% and 63.1%. They were significantly more unfavorable than those in the postoperative CRP/low group, which were 83.3% (p = 0.0142) and 79.0% (p = 0.0075) (Fig. 3 and data not shown).

The factors that were considered in the univariate analysis are summarized in Table 2. The factors that were significantly associated with a limited survival were gender (p = 0.0155), tumor size (p <0.0001), nodal metastasis (p <0.0001), histology (p = 0.0008), adjuvant chemotherapy (p = 0.0001), preoperative WBC count (p = 0.0212), preoperative CRP level (p = 0.0006), and the postoperative CRP level (p = 0.0143). The variable factors were entered into the Cox proportional hazards model by a forward stepwise procedure, and the results of multivariate analysis are summarized in Table 3. A multivariate analysis showed the tumor size (> 3 cm), lymph node metastasis (N1–2), and an elevated preoperative CRP level to demonstrate a significant difference (p = 0.0078, p <0.0001, and p =

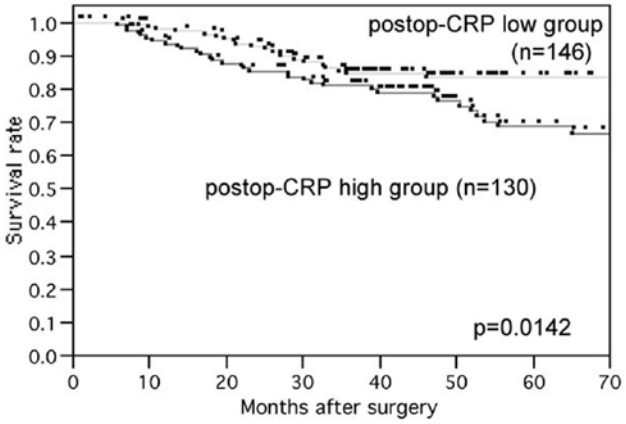

Fig. 3. Disease-specific survival curves for patients with NSCLC (stages I–IIIA) after a curative resection.
Postoperative CRP/high group (n = 130) vs. postoperative CRP/low group (n = 146). The p value was determined using the log-rank test.

Table 2. Univariate analysis of the prognostic factors

Factors	Hazard ratio (95% CI)	p value
Age	1.005 (0.980–1.034)	0.5079
Gender (female vs. male)	1.422 (1.066–1.956)	0.0155
Tumor size (≤ 3 cm vs. > 3 cm)	1.870 (1.437–2.464)	<0.0001
Nodal metastasis (N0 vs. N1–2)	1.719 (1.311–2.236)	0.0001
Histology (adenocarcinoma vs. others)	1.607 (1.228–2.085)	0.0008
Adjuvant chemotherapy (no vs. yes)	1.719 (1.311–2.236)	0.0001
Pre-CRP (< 0.5 mg/dl vs. ≥ 0.5 mg/dl)	1.694 (1.268–2.221)	0.0006
Post-CRP (< 0.5 mg/dl vs. ≥ 0.5 mg/dl) at POD 30	1.385 (1.067–1.819)	0.0143
LDH (≤ 229 U/L vs. > 229 U/L)	1.004 (0.741–1.332)	0.9763
WBC (≤ 9,000/mm^3 vs. > 9,000/mm^3)	1.780 (1.103–2.610)	0.0212

95% CI, 95% confidence interval; CRP, C-reactive protein; POD, postoperative day; LDH, lactate dehydrogenase; WBC, white blood cell.

Table 3. Multivariate analysis of the prognostic factors

Factors	Hazard ratio (95% CI)	p value
Gender (female vs. male)	1.114 (0.811–1.565)	0.5123
Tumor size (≤ 3 cm vs. > 3 cm)	1.448 (1.101–1.931)	0.0078
Nodal metastasis (N0 vs. N1–2)	2.159 (1.562–2.973)	<0.0001
Histology (adenocarcinoma vs. others)	1.104 (0.813–1.486)	0.5207
Adjuvant chemotherapy (no vs. yes)	1.109 (0.786–1.519)	0.5923
Pre-CRP (< 0.5 mg/dl vs. ≥ 0.5 mg/dl)	1.522 (1.065–2.138)	0.0220
Post-CRP (< 0.5 mg/dl vs. ≥ 0.5 mg/dl) at POD 30	1.088 (0.811–1.465)	0.5743
WBC (≤ 9,000/mm^3 vs. > 9,000/mm^3)	1.313 (0.774–2.094)	0.2930

95% CI, 95% confidence interval; CRP, C-reactive protein; POD, postoperative day; LDH, lactate dehydrogenase; WBC, white blood cell.

0.0220, respectively). However, the multivariate analysis showed that the postoperative CRP level was not a significant factor (p = 0.5743).

The patients were then divided into two groups, the preoperative CRP/low group (n = 231) and the CRP/high group (n = 45). As shown in Fig. 4, the serum CRP level in 139 of 231 patients (60.2%) had declined to normal level in the preoperative CRP/low group, whereas the serum CRP level in only 7 of 45 patients (15.6%) had declined to the normal level in the preoperative CRP/

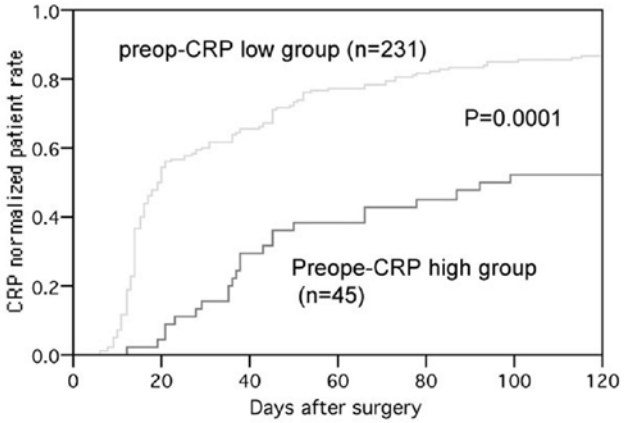

Fig. 4. Rate of CRP normalized patients among patients with NSCLC (stages I–IIIA) after a curative resection.
Preoperative CRP/high group (n = 45) vs. preoperative CRP-low group (n = 23l). The p value was determined using the log-rank test.

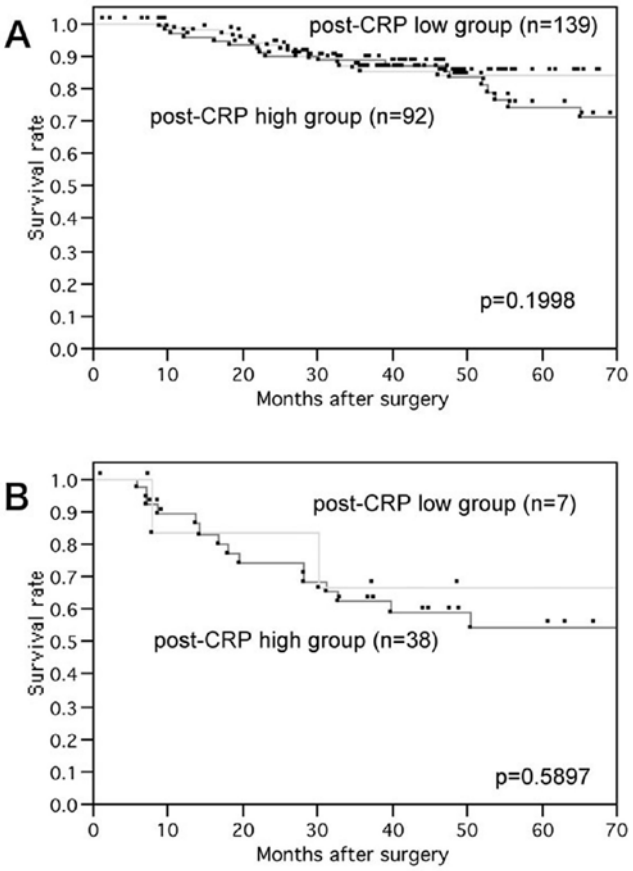

Fig. 5. Disease-specific survival curves for patients with NSCLC (stages I–IIIA) after a curative resection.
Postoperative CRP/high group vs. postoperative CRP/low group among the preoperative CRP/low group (**A**: n = 92 and n = 139, respectively) or the preoperative CRP/high group (**B**: n = 38 and n = 7, respectively). The p value was determined using the log-rank test.

high group (p <0.0001) within 30 days postoperation. The groups were further divided into two subgroups, a postoperative CRP/low and a postoperative CRP/high group. The 5-year disease-specific survival rates of the postoperative CRP/high group and postoperative CRP/low group in the preoperative CRP/low group were 74.8% and 84.0% (p = 0.1998, Fig. 5A). The 5-year disease-specific survival rates of the postoperative CRP/high group and postoperative CRP/low group in the preoperative CRP/high group were 54.3% and 66.7% (p = 0.5897, Fig. 5B).

Discussion

The major finding of this study was that the 5-year disease-specific survival rates and the overall survival rates in the postoperative CRP/low group were significantly higher than those in postoperative CRP/high group in patients with NSCLC after a curative operation. However, the postoperative CRP level was not an independent prognosis indicator.

The disease-specific and overall survival rates in the preoperative CRP/high group were significantly lower than rates in the preoperative CRP/low group (Fig. 1 and data not shown). Based on a multivariate analysis, the preoperative serum CRP level was selected as one of the unfavorable indicators regarding survival; this had been confirmed in a previous study.[6] The rate of postoperative CRP normalized patients in the preoperative CRP/low group was significantly higher than in the preoperative CRP/high group (Fig. 4). Furthermore, there is no 5-year disease-specific survival and overall survival differences between the postoperative CRP/low group and the postoperative CRP/high group when they are divided first into two groups, based on the preoperative CRP data. Taken together, the statistical significant difference of 5-year survival between the postoperative CRP/low group and the postoperative CRP/high group might depend on correlation with the preoperative CRP status.

The postoperative CRP/low group was defined as patients in whom the CRP level was normalized within 30 days postoperation in this study. The postoperative CRP/high/low groups were defined by employing several time points from 30 to 90 postoperative days; the results of the univariate analysis, multivariate analysis, and survival curve significance are consistent with the results (data not shown).

The prognostic value of the CRP levels has been reported

for surgically curative solid cancers, such as lung,[6] liver,[5] esophagus[4,8] and colon cancers.[2,3,9] The mechanism by which cancer is accompanied by increased CRP level is well known. The liver production of CRP is strongly induced by such cytokines as IL-1, tumor necrosis factor (TNF), and mostly IL-6. In contrast, the mechanism for correlation between CRP levels and prognosis in cancer patients remains to be determined. One explanation is that cancer cells can increase the production of inflammatory proteins. Experimental studies in the NSCLC cell lines showed that at least some NSCLC tumors are actually able to produce IL-6,[10,11] IL-8, and TNF-α.[12] If this is true, the survival rate of the postoperative CRP/low group among the preoperative CRP/high group would show good prognosis. In fact, there are several reports that among patients with preoperative high tumor marker levels, those with low levels of postoperative tumor markers, which might be produced by the tumors themselves, have better prognoses than patients with high levels.[13,14] However, the current results show no significant difference between the two groups (Fig. 5B). Jones et al. reported that the serum CRP level is positively correlated with the maximum pathological tumor size, but not the pN stage.[15] They also showed that the incidence of an incomplete resection is higher in the CRP/high group, thus suggesting that the CRP/high group might include latent inoperable patients. Moreover, several reports indicate that CRP levels are associated with lymphovascular invasion, suggesting that the CRP/high group might correlate with cytological tumor spread. Therefore the mechanism that determines the CRP levels may be correlated with the prognosis in cancer patients and may be more complicated.

In conclusion, the present study showed both higher pre- and postoperative serum-CRP levels to be poor prognostic factors. The serum-CRP dosage is a simple, reliable, and reproducible method in which the interpretation of the results is also relatively easy. Therefore the preoperative CRP level, but not the postoperative CRP level, may be a useful adjunct diagnostic modality that can be routinely performed during the screening of patients with NSCLC.

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