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Preoperative Elevation of Serum C-Reactive Protein as an Independent Prognostic Indicator for Gastric Cancer

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Abstract

Purpose. Preoperative elevation of serum C-reactive protein (CRP) is a prognostic indicator for some malignant tumors. We investigated the clinicopathologic importance of an elevated preoperative serum CRP value in gastric carcinoma patients.

Methods. We studied the relationship between the preoperative serum CRP value and clinicopathologic characteristics in 204 patients who underwent curative resection of gastric carcinoma.

Results. The patients with preoperative CRP elevation had significantly poorer survival than those without CRP elevation ($P < 0.0001$). According to multivariate analysis, the factors independently associated with an unfavorable prognosis were a high preoperative CRP value ($P = 0.024$), lymphatic invasion ($P = 0.017$) and advanced tumor stage ($P = 0.016$).

Conclusion. Preoperative serum CRP elevation can be an independent prognostic indicator in patients with gastric carcinoma.

Key words Gastric carcinoma · C-reactive protein · Curative resection · Prognostic indicator

Introduction

C-reactive protein (CRP) is an acute-phase protein, which is synthesized by hepatocytes and increases in the serum in accordance with inflammatory diseases.[1] The serum CRP value has been reported to increase with inflammatory changes in the host. Since Rashid et al.[2] proposed measuring the serum CRP value to investigate the clinical characteristics of patients with gastric carcinoma, many investigations have found that an elevated serum CRP value is an indicator of unfavorable prognosis for patients with malignant tumors, including carcinoma of the gastrointestinal tract.[3–7] However, its implications for individual gastric carcinomas have not been fully studied.

In the current study, we investigated the relationship between the preoperative elevation of serum CRP and the clinicopathologic features of patients with gastric carcinoma to establish its possible significance in relation to the biological aspects of gastric carcinoma.

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Patients and Methods

Patients

The subjects of this study were 204 patients who underwent curative resection of gastric carcinoma in our department between January 1998 and April 2008. Patients who had inflammatory diseases influencing the serum value of serum CRP, including infection and collagen disease, and those with primary cancers in other organs were excluded from the study. None of the patients enrolled in the study had received induction therapy.

Clinicopathologic Investigation

The clinicopathologic factors were based on the Japanese Classification of Gastric Carcinoma, as outlined by the Japanese Gastric Cancer Association.[8] Clinicopathologic data were compared between patients with and those without an elevated preoperative serum CRP value.

Measurement of Serum CRP

Serum was collected 1–2 days before the operation, to measure the CRP value, which was done once for each patient. Assays were performed by medical technicians who were unaware of the clinical information about the patients enrolled in the study. Serum CRP was measured by latex photometric immunoassay[9] using a CRP-L kit (Yatoron, Tokyo, Japan). According to the

manufacturer's instructions, the normal range for the serum CRP value is 0–5 mg/l. Hence, a serum CRP value higher than 5 mg/l was considered positive.

Follow-Up of the Patients

Patients were followed up until their death and only patients who died of gastric carcinoma were included in the tumor-related deaths. Follow-up after surgery ranged from 60 days to 9 years 1 month.

Statistical Analysis

The chi-squared test, Student *t*-test and Mann–Whitney test were used to compare the data. Survival curves were created using the Kaplan–Meier method, and the Mantel–Cox test was used to analyze the equality of the survival curves. We used a Cox proportional hazards model for the multivariate analysis to establish the independent prognosticators. A P value of less than 0.05 was considered significant.

Results

The patients ranged in age from 27 to 89 years, with a median age of 67 years. There were 142 men and 62 women. Forty-three patients had an elevated preoperative serum CRP value (Group H-CRP; 21.1%), and 161 did not (Group L-CRP; 78.9%). Table 1 shows the rela-

Table 1. Relationship between serum C-reactive protein (CRP) elevation and the clinicopathologic features of patients with gastric carcinoma

	Group H-CRP (n = 43)	Group L-CRP (n = 161)	P value
Sex			
Male	33 (23.2)	109 (76.8)	0.084
Female	10 (16.1)	52 (83.9)	
Age (years)	70.4 ± 9.2	66.3 ± 10.7	0.052
Location of tumors			
Upper	9 (30.0)	21 (70.0)	0.185
Middle	20 (16.8)	99 (83.2)	
Lower	14 (25.5)	41 (74.5)	
Gross type[a]			
Type 0	12 (11.2)	95 (88.8)	0.0008
Type 1, 2	13 (30.8)	34 (69.2)	
Type 3, 4	18 (41.1)	32 (58.9)	
Histology[b]			
Well	8 (14.0)	49 (86.0)	0.412
Moderate	11 (26.3)	38 (73.7)	
Undifferentiated	24 (29.7)	74 (70.3)	
Depth of tumor			
T1	10 (11.2)	95 (88.8)	<0.0001
T2	26 (29.5)	62 (70.5)	
T3	7 (63.6)	4 (36.4)	
Lymph node metastasis			
Positive	27 (35.5)	49 (64.5)	0.0001
Negative	16 (12.5)	112 (87.5)	
Lymphatic invasion			
Positive	26 (28.0)	67 (72.0)	0.028
Negative	17 (15.3)	94 (84.7)	
Venous invasion			
Positive	19 (44.2)	24 (55.8)	<0.0001
Negative	24 (14.9)	137 (85.1)	
Tumor stage			
IA	10 (10.3)	87 (89.7)	0.0004
IB	6 (17.6)	28 (82.4)	
II	14 (35.9)	25 (64.1)	
IIIA	8 (30.8)	18 (69.2)	
IIIB	5 (62.5)	3 (37.5)	

H-CRP, high CRP level; L-CRP, low CRP level

[a] Type 0, superficial tumor; type 1, polypoid; type 2, ulcerating circumscribed; type 3, ulcerating infiltrative; type 4, diffusely infiltrative

[b] Well, well-differentiated adenocarcinoma; Moderate, moderately differentiated adenocarcinoma; Undifferentiated, poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma

tionship between the serum elevation of CRP and the clinicopathologic characteristics of these restricted patients. Significant differences were found in the gross type of the tumors ($P < 0.0001$), depth of tumor invasion ($P < 0.0001$), lymph node metastasis ($P = 0.0001$), lymphatic invasion ($P = 0.028$), venous invasion ($P < 0.0001$), and stage of the tumor ($P = 0.0004$). The 1-, 3-, and 5-year survival rates of Group H-CRP were 88.0%, 65.4%, and 54.5%, respectively, which were significantly worse than those of Group L-CRP (97.8%, 95.0%, and 87.9%, respectively, $P < 0.0001$; Fig. 1).

Multivariate analysis revealed that the factors independently associated with an unfavorable prognosis were an elevated preoperative CRP value ($P = 0.024$) as well as lymphatic invasion ($P = 0.017$) and more advanced tumor stage ($P = 0.016$; Table 2).

Discussion

C-reactive protein is upregulated by such proinflammatory cytokines as interleukin-1 (IL)-1, IL-6, and tumor necrosis factor (TNF), and the production of these cytokines in the microenvironmental circulation has been reported to promote the synthesis of CRP in hepatocytes.[10] C-reactive protein might also be expressed in selected tumor cells.[11] Based on the findings of many investigations, it is now widely accepted that an elevated serum CRP value is a reliable indicator of a poor prognosis for certain malignant tumors, including carcinomas of the lung,[12] prostate,[13] and ovary,[14] other than tumors of the gastrointestinal tracts.

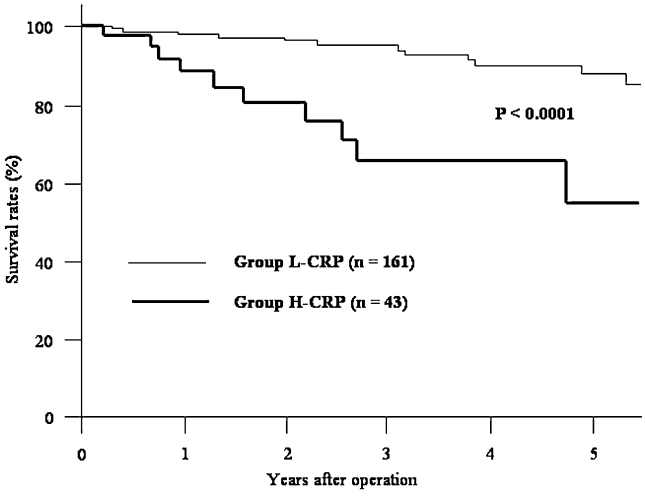

Fig. 1. Survival curves. Patients with an elevated serum C-reactive protein value (*H-CRP*, *bold line*) had a significantly poorer 5-year survival rate than those without an elevated serum CRP value (*L-CRP*, *thin line*), at 54.5% vs 87.9% ($P < 0.0001$)

The findings of our original investigation in 1998 suggested that an elevated serum CRP value was a possible indicator of malignant potential in colorectal carcinoma.[5] We recently presented additional results showing its significance as an independent prognosticator,[4] and evidence of its significance as an independent prognostic indicator in esophageal carcinoma was also shown.[7]

Recent investigations suggest that elevations of serum IL-6[15,16] and TNF[17] could be sensitive prognostic indicators in gastric carcinoma. Therefore, an elevated serum CRP value, being regulated by these cytokines, might contain biological evidence of malignant potential in gastric carcinoma. However, the clinicopathologic significance of an elevated CRP value in patients with gastric carcinoma has not been investigated sufficiently.

A major objective of our series of investigations[4,5,7] was to establish a simple and useful marker to reflect the biological potential of malignant tumors of the gastrointestinal tract. The serum CRP level, which can be measured instantly at low cost, may provide valuable information predictive of the outcome of patients with gastric carcinoma.

The concentration of acute-phase response proteins, including CRP, increases with the cachexia associated with very advanced tumors.[18] However, our multivariate analysis of patients treated with curative resection revealed that the factors independently associated with a worse prognosis of gastric carcinoma were not only tumor-related, such as lymphatic invasion and tumor stage, but also related to the preoperative elevation of serum CRP.

In conclusion, the preoperative elevation of serum CRP was found to be an independent prognostic indicator for patients with gastric carcinoma. The serum value of CRP can be measured in most institutes and could thus be a global marker to predict the outcome of patients with gastric carcinoma.

Table 2. Factors independently associated with the prognosis of patients with gastric carcinoma

Variables	Regression coefficient	Standard error	OR (95% CI)	*P* value
Lymphatic invasion	1.454	0.603	4.274 (1.311–13.89)	0.017
Tumor stage tumors	1.123	0.496	3.077 (1.161–8.130)	0.016
Preoperative elevation of serum CRP	1.080	0.455	2.941 (1.208–7.194)	0.024

OR, odds ratio; CI, confidence interval

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