Preoperative Serum C-reactive Protein and Gastric Cancer; Clinical-pathological Correlation and Prognostic Significance

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Background: C-reactive protein (CRP) is a widely-used systemic biomarker for inflammation. Serum CRP is elevated in many malignancies, and is also a prognostic indicator of malignant potential. However, the prognostic significance for survival from gastric cancer has not yet been clarified. We studied the clinical-pathologic association and prognostic significance of preoperative serum CRP in gastric cancer patients.

Methods: A total of 170 gastric cancer patients were included in this study. The mean age of the patients was 65.1 years (range, 29-89), and 112 were men. All gastric cancer patients had undergone gastric resection. The serum CRP levels of patients before the operation along with those from 405 healthy controls were measured by a high sensitivity CRP test.

Results: The 95th percentile value (= 3.0 mg/L) of the serum CRP data in 405 healthy controls was set as the upper cut-off value of the normal range. Abnormally high levels of serum CRP were observed in 65 (38.2%) of our 170 patients in contrast to only 20 (4.9%) of the 405 healthy controls ($p < 0.001$). Elevated CRP was associated with older age ($p = 0.009$), grossly infiltrative type ($p = 0.001$), larger tumors ($p < 0.001$), serosal invasion ($p = 0.001$), lymph node metastasis ($p < 0.001$), distant metastasis ($p = 0.017$), and lymphatic invasion ($p = 0.002$). Overall, a higher CRP level was strongly parallel to a pathologically more advanced stage ($p = 0.001$). The 5-yr survival rate of patients with an elevated (> 3.0 mg/L) CRP was significantly worse than those without (≤ 3.0 mg/L) (27.1% versus 54.1%, log rank $p = 0.0010$).

Conclusion: The preoperative serum CRP level was abnormally elevated in 38.2% of gastric cancer patients. Elevated CRP was associated with progressive disease or an advanced stage, and a worse survival. Although serum CRP is not a specific biomarker for gastric cancer, it might be a potential prognostic biomarker and a promising therapeutic target for gastric cancer patients.

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Key words: C-reactive protein, inflammatory biomarker, prognostic factor, gastric cancer

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Gastric cancer was the 5th leading cause of cancer death in Taiwan in 2007, and the second worldwide.[1,2] Its incidence has markedly declined over the past decades especially in developing countries. The reasons for this decrease are unknown, but are possibly related to (1) improved storage of food, decreased intake of salted or preserved foods, and increased consumption of fresh fruits and vegetables, and (2) a lower rate of *H. pylori* infection as a result of improving hygienic conditions and increased use of antibiotics.[2] A high rate of early gastric cancer in Japan was found in a national mass survey.[3] Nevertheless, the prognosis for advanced gastric cancer remains poor when curative resection is not feasible.[4] To improve the poor survival outcome and permit earlier diagnosis, there is a need for new and more sensitive biomarkers than currently available tumor markers such as carcinoembryonic antigen and CA19-9.[5]

In the past two decades numerous biomarkers of gastric cancer have been explored and identified using advanced technologies in molecular biology, such as DNA microarray and proteomics.[6] They have contributed to our knowledge of the molecular and cellular mechanisms of gastric carcinogenesis and progression. Most of them are prognostic factors used to indicate groups of patients at risk of relapse or metastasis.[6] Biomarkers for the early detection of gastric cancer and monitoring of therapeutic efficacy are still lacking.

C-reactive protein (CRP) was first discovered in the plasma of patients during the acute phase of pneumococal pneumonia. It was named for its high binding affinity to the C-polysaccharide of *Streptococcus pneumonia*.[7] CRP appears in the peripheral blood after it is produced by the liver in response to inflammatory cytokines such as intereukin (IL)-1, tumor necrosis factor (TNF)-α, and in particular IL-6, within a few hours following insults such as infection, trauma, or myocardial infarction.[8] Therefore, it is a very useful systemic marker in the presence of inflammation and infection.[9]

In the past 10 years, the clinical importance of serum CRP has been reemphasized for cardiovascular diseases. The introduction of a high sensitivity technique has enabled the detection of a minor elevation of CRP that can help predict patients at high risk for cardiovascular diseases in an apparently healthy population.[9,10] CRP elevation has also been associated with a number of diseases including metabolic syndrome, autoimmune diseases, inflammatory diseases (e.g. Crohn's disease, rheumatoid arthritis), and malignancies.[11]

In several prospective cohort studies, elevated CRP was associated with an increased risk of malignancies such as colorectal, lung, and breast cancers.[12] The prognostic significance of serum CRP has been demonstrated in a variety of primary malignancies, including esophageal, gastroesophageal, colorectal, hepatocellular, pancreatic, prostate, urinary bladder, ovarian and cervical cancers.[13-22] Elevated CRP is associated with progressive disease and worse survival for patients with these malignancies. Serum CRP is an independent prognostic factor for survival after surgical resection of these cancers.[13-22]

Elevation of preoperative CRP has been demonstrated in gastric cancer patients compared with healthy controls.[23-27] Higher CRP levels are significantly associated with progressive disease such as lymph node metastasis, more advanced stage or non- resectable disease in patients with gastric cancer.[23,24,27] Yet, the prognostic significance of preoperative CRP on long-term survival is not yet known for gastric cancer. This prospective study investigated the prognostic significance of preoperative CRP and survival outcome after a long-term follow-up of patients with gastric cancers.

METHODS

Subjects

A total of 170 patients who underwent gastrectomy with gastric cancer, between 2000 and 2001, were enrolled. The median age was 65.1 years (range, 29-89) with a ratio of men to women of 112/58. The controls were 405 healthy volunteers, 204 men and 201 women.

Serum samples

The peripheral venous blood of patients was withdrawn one day before surgery. That of healthy controls was done on the day of a health check-up. The blood samples were temporarily stored at 4°C in a tumor bank. Immediately after the blood was centrifuged, serum samples or the supernatant were frozen and stored at –40°C until use.

Measurement of the serum CRP level

The stored sera of both the patients and healthy controls were used for a high sensitivity (hs) CRP test. All measurements were performed in a single batch. Serum CRP was measured using the N High-Sensitivity CRP mono assay with the automated BN ProSpec Nephelometer (Dade Behring, Deerfield, Illinois, U.S.A.). The test can detect levels as low as 0.08 mg/L and covers CRP concentrations only up to 40 mg/L. For patients with a CRP value > 40 mg/L, samples were automatically diluted to measurable concentrations.

Surgery

Subtotal and total gastrectomies were performed for 117 and 53 patients, respectively. Curative resection required cancer-free resection margins, accompanied by a D2 systemic lymphadenectomy (dissection of level 1 and 2 regional lymph nodes), and combined resection of neighboring organs if invaded.[28] According to the UICC's classification of residual tumors, curative resection with no residual tumor (R0) was achieved in 122 (71.8%) of the patients.[29] Surgery with microscopic residual tumors (R1) was performed for 5 (2.9%) patients and surgery with macrosopic residual tumors (R2) for 43 (25.3%). The reason for R1 resection was mainly positive section margins which could not be further resected because of technical difficulty, or patient refusal of more extended surgery. R1 and R2 resections were thus non-curative or palliative.

Postopertive chemotherapy

Chemotherapy was performed if the patient consented and the performance status was less than or equal to 3. Adjuvant chemotherapy was performed for patients after curative (R0) resection if the surgical pathology showed serosal invasion (T3 or T4) or lymph node metastasis. The regimens of adjuvant chemotherapy in the first 6 months postoperatively consisted of mitomycin and an oral 5-FU, mainly UFUR®, a fluoropyrimidine analogue. Therapeutic chemotherapy was performed for those with stage 4 disease or residual tumors after palliative (R1 or R2) resection. The regimens of therapeutic chemotherapy were diverse. They could be categorized into 5-flurouracil (5-FU)-based and cisplatin-based regimens. The most frequently used regimen was a combination of 2600 mg/m^2%-FU and 150 mg leucovorin through an infusion pump.

Clinical-pathological studies

Resected specimens were studied pathologically according to the criteria described in the Japanese General Rules for Gastric Cancer Study[28] and the AJCC's pTNM classification.[29] The study items included age, gender, tumor location, tumor size (maximal diameter), gross (Borrmann) type, depth of wall invasion, resection margin, histologic type, lymph node metastasis, vascular invasion, lymphatic invasion, perineural invasion and residual disease after resection (R-classification). The histological features were classified into 2 types, (1) the intestinal or differentiated type, consisting of papillary and tubular adenocarcinomas, and (2) the diffuse or undifferentiated type, consisting of poorly differentiated, signet-ring cell, and mucinous adenocarcinomas. After discharge, all patients received periodic follow-up in the outpatient department until the time of manuscript preparation or patient death.

Statistical analysis

The serum CRP data are presented as the median and interquartile range (25th ~75th percentiles). The cut-off level or the upper level of normal of the serum CRP was taken at the 95th percentile of data in our healthy control group by hs CRP test.[30] When appropriate, the Mann-Whitney U test (for two groups) or Kruskal Wallis test (for more than two groups) was used for between-group comparisons. Only 4 patients were lost to follow up. Patient survival was expressed by cumulative 5-year survival rates. The cancer-specific survival outcome was expressed by applying the Kaplan-Meier method for all patients excluding those who died of surgical complications or non-cancer related deaths (n = 8 or 4.7%). The log-rank test was used to compare the prognostic significance of individual variables on survival. Cox's proportional hazards model was used in multivariate analysis to identify the independent predictors of survival. A p value of < 0.05 was considered statistically significant. In multiple comparisons, however, the significance level, α was adjusted to avoid a type 1 error and to retain an overall significance level of 0.05 by using the Bonferroni correction, where the adjusted α level was equal to 0.05 divided by the number of tests or comparisons. The adjusted α level is noted in the text wherever neces-

sary.

RESULTS

Comparison of serum CRP levels between gastric cancer patients and healthy controls

Fig. 1 show the histograms of the CRP data from the healthy controls (n = 405) and gastric cancer patients (n = 170), respectively. Both histograms demonstrated that the distribution of the CRP data in both groups was asymmetric (skew). Therefore, the median and interquartile range were applied to express the data. The median of the serum CRP levels in the healthy controls (n = 405) and gastric cancer patients (n = 170) were 0.58 mg/L (interquartile range, 0.30-1.21), and 1.60 mg/L (interquartile range, 0.61-5.30), respectively, with a significant difference ($p < 0.001$). An extremely high level of CRP was found only in the patient group (Fig. 2). The upper normal level or cut-off value of the serum CRP was set at the 95th percentile (= 3.0 mg/L) of the healthy control group.[30] Elevation of the CRP level (≥ 3 mg/L) was observed in 65 (38.2%) of our 170 patients in contrast to only 20 (4.9%) of the 405 healthy controls ($p < 0.001$). The sensitivity, specificity, positive predictive value and negative predictive value for CRP as a diagnostic test for gastric cancer in this study were 38.2% (65/170), 95.1% (385/405), 76.5% (65/85), and 78.6% (385/490), respectively.

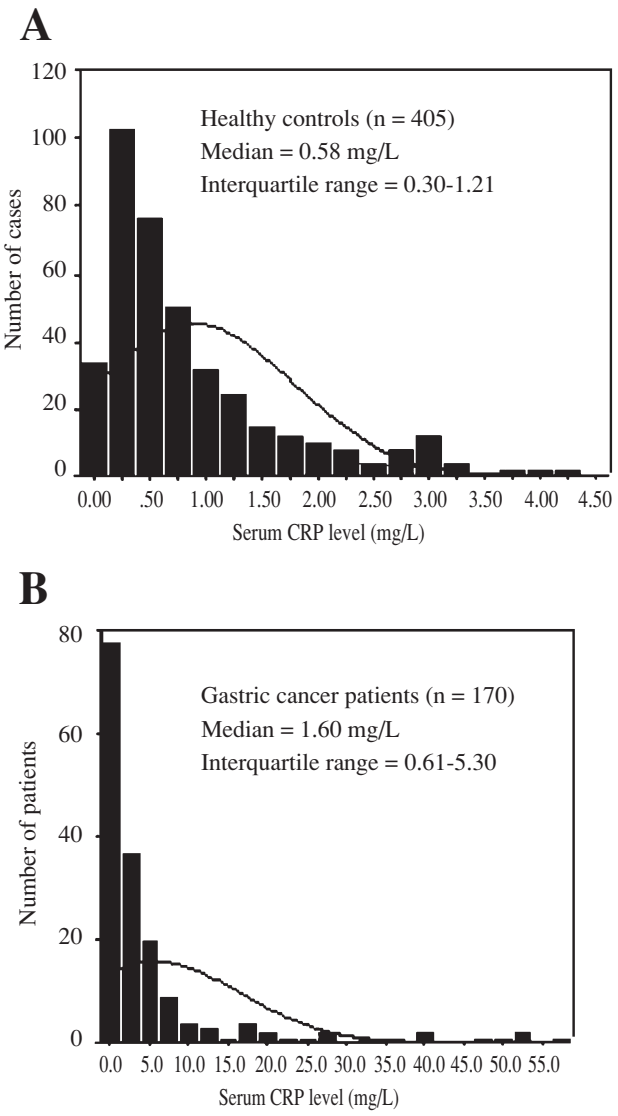

Fig. 1 Histograms for serum CRP data from (A) the healthy controls (n = 405) and (B) gastric cancer patients (n = 170) in our study. Normal curves were added as references to the histograms with the same data. Both histograms show a skew or asymmetric distribution. Therefore, the median and interquartile range were used to express the data.

Clinical-pathological correlation

The Table 1 shows the association of the serum level of CRP with clinical-pathological parameters. It was positively associated with old age (> 65 years) ($p = 0.009$; Boniferroni's adjusted α level = 0.025),

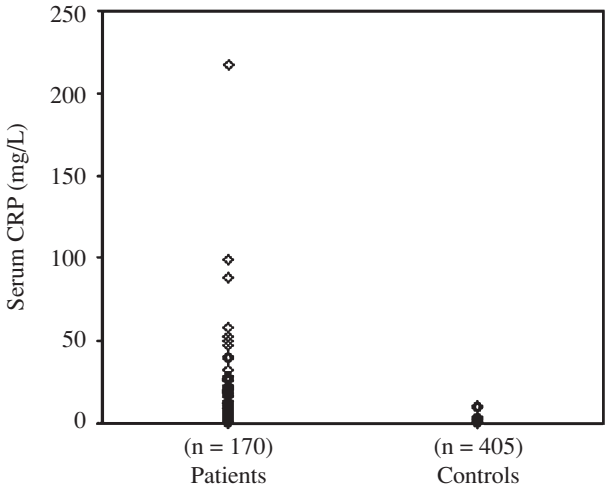

Fig. 2 Scatter plots of preoperative CRP in patients with gastric cancer (n = 170) and in healthy controls (n = 405). There was a significant difference between them ($p < 0.001$). Abnormally high level of CRP was found only in the patient group.

Table 1. Patient Characteristics, Clinicopathological Correlations of Serum CRP Level and 5-Year Survival Rate in 170 Patients with Gastric Cancer

Parameters	No.	Serum CRP*	*p* value†	5-yr S.R.‡	Logrank *p*§
Age (yrs)					
≦ 40	11	0.96 (0.59-4.05)	0.009	45.5	0.3913
41~65	75	1.01 (0.43-4.09)		50.4	
≧ 66	84	2.47 (0.86-6.45)		36.8	
Gender					
Male	112	1.96 (0.65-5.82)	0.289	41.6	0.2772
Female	58	1.12 (0.53-4.30)		47.2	
Gross (Borrmann) type					
Localized (1,2)	50	0.78 (0.39-2.14)	0.001	68.5	< 0.0001
Infiltrative (3,4)	120	2.01 (0.83-5.82)		33.8	
Location in stomach					
Proximal	36	2.15 (0.61-6.50)	0.695	26.7	0.0086
Middle	38	1.07 (0.58-4.02)		42.7	
Distal	94	1.57 (0.60-5.14)		50.1	
Entire	2	8.94 (0.34-)		0	
Maximal diameter (cm)					
0.1~2	25	0.70 (0.29-1.99)	< 0.001	70.8	< 0.0001
2.1~5	79	1.16 (0.47-3.93)		54.8	
5~	66	3.22 (0.91-8.70)		18.5	
Histologic type					
Intestinal	66	1.49 (0.62-5.01)	0.568	53.0	0.0621
Diffuse	104	1.77 (0.53-6.70)		36.9	
Depth of wall invasion (pT)					
T1	27	0.64 (0.16-2.17)	< 0.001	81.5	< 0.0001
T2	17	0.92 (0.49-1.74)		80.4	
T3	100	1.65 (0.65-5.51)		34.6	
T4	26	4.04 (1.72-23.17)		12.5	
Serosal invasion					
No	44	0.84 (0.31-2.05)	0.001	81.2	< 0.0001
Yes	126	2.02 (0.78-6.70)		29.9	
Lymph node metastasis (pN)					
N0	50	0.81 (0.32-1.63)	< 0.001	86.0	< 0.0001
N1	61	2.01 (0.57-5.82)		33.9	
N2	29	2.46(0.86-13.80)		23.7	
N3	30	3.19 (1.08-8.49)		3.7	
Lymph node metastasis					
No	50	0.81 (0.32-1.63)	< 0.001	86.0	< 0.0001
Yes	120	2.44 (0.80-7.10)		24.0	
Liver metastasis					
No	165	1.57 (0.58-5.23)	0.140	45.0	< 0.0001
Yes	5	3.19 (1.39-49.45)		0.0	

Table 1. Patient Characteristics, Clinicopathological Correlations of Serum CRP Level and 5-Year Survival Rate in 170 Patients with Gastric Cancer (Continued)

Parameters	No.	Serum CRP*	*p* value†	5-yr S.R.‡	Logrank *p*§
Peritoneal seeding					
No	149	1.56 (0.60-5.01)	0.065	49.0	< 0.0001
Yes	21	3.22 (0.63-22.63)		5.0	
Distant metastasis					
No	132	1.48 (0.48-5.11)	0.017	55.4	< 0.0001
Yes	38	2.81 (0.89-11.04)		2.8	
pStage					
I	36	0.84 (0.22-1.80)	0.001	88.8	< 0.0001
II	21	1.16 (0.43-4.59)		65.2	
III	70	2.31 (0.78-6.70)		35.5	
IV	43	2.42 (0.85-10.72)		4.9	
Stage I-II	57	0.88 (0.34-2.04)	< 0.001	80.4	< 0.0001
Stage III-IV	113	2.42 (0.81-7.66)		23.5	
Vascular invasion					
No	146	1.49 (0.60-5.23)	0.389	48.6	< 0.0001
Yes	24	3.09 (0.57-5.50)		10.6	
Lymphatic invasion					
No	81	1.06 (0.43-3.09)	0.002	62.7	< 0.0001
Yes	89	2.25 (0.77-7.31)		24.7	
Perineural invasion					
No	97	1.28 (0.60-4.50)	0.253	54.4	0.0008
Yes	73	2.05 (0.58-7.70)		28.2	
H. pylori infection					
Present	34	1.54 (0.48-5.29)	0.672	55.7	0.2731
Absent	136	1.59 (0.58-5.22)		40.8	
Residual tumors (R)					
R0	122	1.45 (0.49-5.18)	0.072	59.5	< 0.0001
R1	5	1.80 (0.23-3.90)		0	
R2	43	2.42 (0.85-10.72)		2.4	
Serum CRP					
< 3.0 mg/L‖	105	0.78 (0.41-1.41)	< 0.001	54.1	0.0010
≧ 3.0 mg/L	65	7.74 (4.76-20.86)		27.1	
Serum CRP					
< 1.60 mg/L¶	85	0.61 (0.34-0.91)	< 0.001	56.8	0.0011
≧ 1.60 mg/L	85	5.24 (3.07-12.27)		30.2	

Abbreviations: CRP: C-reactive protein; *: In ng/mL (median [interquartile range; 25th -75th percentiles]); †: Mann-Whitney U test (for 2 groups) or Kruskal Wallis test (for > 2 groups); ‡: Five-year survival rate; §: Log rank test; ‖: The cut-off value at the 95 percentile of CRP data in healthy controls; ¶: The cut-off valule at the median of CRP data in patient group.

the gross appearance (Borrman type) (p = 0.001), tumor size (maximal diameter) (p < 0.001; Boniferroni's adjusted α level = 0.025), depth of wall invasion (p < 0.001; Boniferroni's adjusted α level = 0.0167 for pT), lymph node metastasis (p < 0.001; Boniferroni's adjusted α level = 0.0167 for pN), and distant metastasis (p = 0.017). It was closely associated with lymphatic invasion (p = 0.002), but not vascular invasion (p = 0.389) or perineural invasion (p = 0.253). Overall it was associated with the pathological stage (p = 0.001; Boniferroni's adjusted α level = 0.0167 for pStage). It was not associated with gender (p = 0.289), tumor location (p = 0.695), or histological type (p = 0.568).

Preoperative serum level and survival outcome

The mean duration of follow up for the survivors (n = 67) was 76.8 months (range, 39-113 months). In all, 92 patients died as a result of progression of gastric cancer, 8 patients died because of surgical complications, and three died of non-cancer causes. The overall cumulative 5–year survival rate of the 170 patients with gastric resection was 44.2%. If the patients were divided into 2 groups according to the 95th percentile (= 3.0 mg/L) as a cut-off value, the 5-year survival rate for the elevated CRP group (n = 105) was significantly worse than that of the non-elevated group (n = 65) (27.1% versus 54.1%; log rank p = 0.0010) (Fig. 3). When the patients were divided into two equal groups according to the median CRP level (= 1.60 mg/L) in the patient group as a cut-off value, the 5-year survival rate of the elevated CRP group was also significantly worse than that of the non-elevated group (30.2% versus 56.8%; log rank p = 0.0011).

The Table 1 also lists the results of univariate analysis of prognostic significance in our 170 patients. It included the gross appearance, tumor size (maximal diameter), depth of wall invasion, lymph node metastasis, distant metastasis, peritoneal seeding, liver metastasis, pathologic stage, vascular invasion, lymphatic invasion, R-classification of resection (log rank p < 0.0001 in all preceding variables; Boniferroni's adjusted α level = 0.025 for tumor size and R-classification; Boniferroni's adjusted α level = 0.0167 for depth of wall invasion--pT, lymph node metastasis --pN, and pathological stage--pStage), perineural invasion (log rank p = 0.0008), tumor location (log rank p = 0.0086), and elevation of

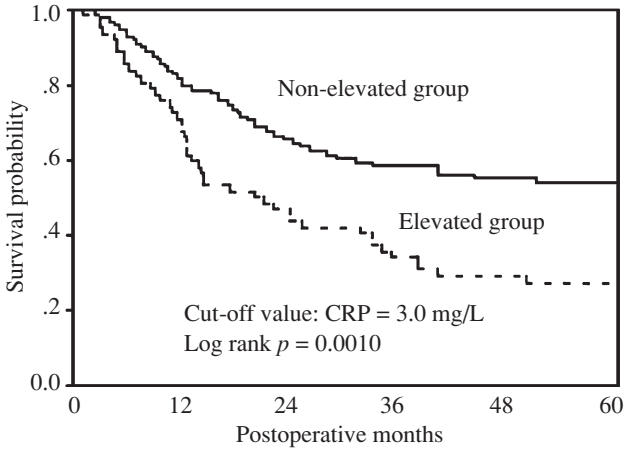

Fig. 3 Kaplan-Meier survival curves for gastric cancer patients with a serum CRP level above (elevated group) and below (non-elevated group) the cut-off value at 3 mg/L, which was the 95th percentile of serum CRP data in 405 healthy controls. The five-year survival rate of the elevated group (n = 105) was significantly better than that of the non-elevated group (n = 65) (27.1% versus 54.1%; log rank p = 0.0010).

serum CRP, with the cut-off value either at the 95th percentile (CRP = 3.0 mg/L) of the healthy controls or at the median (CRP = 1.6 mg/L) of the patients (log rank p = 0.0010 and log rank p = 0.0011, respectively). The age, gender, and histological type were not of significance. Postoperatively, almost all our patients received adjuvant or therapeutic chemotherapy as indicated according to their performance status and pathological stages. Thus, the results of postoperative chemotherapy are not listed in the Table 1 because the indications for chemotherapy were stage-dependent and the practice was not a randomized control study. Multivariate analysis revealed that lymph node metastasis and distant metastasis remained significantly associated with cancer-specific survival, and serum CRP was excluded as an independent prognostic factor.

DISCUSSION

Serum CRP is a very sensitive indicator of current disease activity for inflammation. It has been the most widely used in the clinical diagnosis of acute or chronic inflammation.[9] The measurement of the serum CRP level is simple, cheap, and routinely available in common practice. The introduction of a

high sensitivity technique (hs CRP) has enabled the identification of a group of patients with chronic inflammation, such as those at risk of cardiovascular disease, which manifests only a minor elevation of CRP.[10]

Elevated serum CRP in patients with malignancy is probably a body response secondary to tumor necrosis, local tissue damage and associated inflammation.[31] CRP is produced in hepatocytes as a systemic response to the cytokines released from leukocytes infiltrating within the tumor microenvironment, in particular IL-6.[32] IL-6 may also indirectly influence the binding of CRP to phospholipids on tumor cells, activating the classical C1q pathway of the complement system acting as an opsonin, which may sometimes lead to tumor cell lysis.[33] Thus, CRP is not only a response to the tumor microenvironment, but it may also contribute to disposing of the tumor cell whether it is alive or dead.

Preoperative CRP was higher in gastric cancer patients than in healthy controls in past reports and ours.[23-27] Elevated CRP was significantly parallel to cancer progression and advanced stage in these series as well as in ours.[23,24,27] It is recognized that preoperative elevated CRP is associated with a worse survival in patients with other malignancies besides gastric cancer in the literature.[13-22] Our data from long term follow-up clearly demonstrated that the survival outcome was significantly worse in patients with elevated CRP, the same finding as in other malignancies.

Following potentially curative surgery, the serum CRP usually falls to normal levels in patients with an elevated concentration before the operation.[31] On the contrary, if the postoperative CRP remains high following non-curative surgery, the most plausible cause should be volume loading of residual tumor. Thus, CRP may be useful for postoperative evaluation of treatment effect or recurrence after curative surgery. In the immediate postoperative period, the postoperative CRP level may also vary, depending on the degree of surgical stress or the invasiveness of the surgical procedures; for example, the CRP level should be lower after a laparoscopic gastrectomy than after an open procedure.[34,35] An elevated CRP level may also indicate surgical infection or complications; thus, it is also a useful early sign of post-surgical complications in gastric cancer patients.[36,37]

The linkage between inflammation and cancer was first reported by Rudolf Virchow in 1863. Virchow identified leucocyte infiltration in neoplastic tissues and suggested these sites of chronic inflammation were the origin of cancer.[38] The relationship between Helicobacter pylori bacterial infection and gastric cancer is a typical example of Virchow's hypothesis. *H. pylori* infection can induce acute or chronic gastritis characterized by a marked infiltration of polymorphonuclear leukocytes, macrophages, and lymphocytes in the gastric mucosa. Most patients with *H. pylori* infection have mild or no dyspeptic symptoms, but some patients develop peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma, the so-called MALToma. The epidemiologic link between *H. pylori* and gastric cancer was first pointed out in 1991.[39] *H. pylori* seropostivity was strongly associated with subsequent development of gastric cancer in the non-cardia portion in a meta-analysis of prospective cohorts.[40] It is believed that gastric cancer develops after the gastric mucosa passes through a sequence of histological changes from active gastritis, through atrophy, intestinal metaplasia, dysplasia, and adenocarcinoma.[41]

The molecular mechanisms of response of the local immune response to *H. pylori* infection are complex. There is evidence that *H. pylori* infection induce cytokine (IL-1β, IL-2, IL-6, IL-8, IL-23 and IL-17 and TNF-α, etc) release from both immune and non-immune cells.[42,43] These cytokines enhance CRP production from hepatocytes in infected patients, contributing to amplification of the ongoing inflammation. CRP is not an effective marker for primary diagnosis or post-eradication follow-up of active *H. pylori* infection.[26,44] Furthermore, CRP levels were not different between *H. pylori*-infected and non-infected groups in patients with gastric cancer in other studies and ours.[26,45] Successful eradication of *H. pylori* may cause precancerous lesions to regress.[46] However, the benefit in gastric cancer prevention is limited to patients without atrophy or metaplasia at the start of therapy.[47]

Another frequently mentioned systemic inflammatory marker is cyclooxygenase-2 (COX-2), a local expression of inflammation in tumor tissues.[20] COX-2 is overexpressed in the gastric mucosa in patients with *H. pylori*-induced gastritis or gastric cancer.[47] Through toll-like receptors, *H. pylori* infection also

activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen activated protein kinase (MAPK) pathways for local COX-2 expression in gastric epithelial cells to accelerate inflammation.[48] *H. pylori* eradication may reduce COX-2 expression in *H. pylori* gastritis before the development of intestinal metaplasia.[49]

CRP has been a promising therapeutic target in cardiovascular therapy.[50] Drugs used in the treatment of cardiovascular diseases which are able to lower serum CRP levels include COX inhibitors (aspirin, celecoxib, and etc), platelet aggregation inhibitors, lipid-lowering agents (statins), β-adrenoreceptor antagonists, antioxidants (vitamin E), and angiotensin converting enzyme inhibitors.[50] Since elevated CRP is demonstrated in patients with malignancy, CRP-lowering drugs should theoretically be effective in cancer prevention and therapy. Among those drugs, only COX inhibitors and lipid-lowering agents (statins) provide promising efficacy in gastric cancer prevention therapy.[51,52] COX-2-selective inhibitors, as well as *H. pylori* eradication regimens, may be potentially effective in stopping the progression of gastritis to gastric cancer.[40,52]

In conclusion, CRP, a systemic inflammation marker, is reintroduced as a tool in monitoring malignancies, similar to its use in cardiovascular diseases in recent decades. The measurement of serum CRP is simple, cheap, and routinely available in common practice. Our studies revealed preoperative CRP is significantly associated with progressive disease and survival of gastric cancer patients. Serum CRP might be a potential prognostic biomarker and a promising therapeutic target for gastric cancer patients in the future.

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C- 反應性蛋白質在胃癌病人之臨床病理關聯和預後影響

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背 景： C-反應性蛋白質 (CRP) 是一種被廣泛使用做爲人體發炎的全身性生物標記。於許多癌症病人的血清呈現上升的現象，並且是惡性潛能的一種預後指標。不過 CRP 於胃癌病人的預後影響特別是長年存活，目前仍然不明。本文研究胃癌病人手術前血清 CRP 和其臨床病理的關聯及預後的影響。

方 法： 本研究包括 170 位胃癌接受胃切除手術的病人，有 112 位男性和 58 位女性。平均年齡是 65.1 歲 (範圍 29-89 歲)。這些病人的手術前和另外 405 位健康的控制組的血液都接受高敏感度 CRP 檢驗。

結 果： 以 405 位健康控制組的 95 百分位數 (CRP = 3.0 mg/L) 當做正常上限值，則 170 位胃癌病病人中有 65 位 (38.2%) 的血清 CRP 有不正常的升高，此和健康控制組呈有意義差別 ($p < 0.001$)。CRP 升高和以下幾個因子有密切的關係：高齡 ($p = 0.009$)、肉眼侵潤型 ($p = 0.001$)、腫瘤較大者 (≥ 5 cm) ($p < 0.001$)、侵犯漿膜者 ($p = 0.001$)、淋巴結轉移 ($p < 0.001$)、遠處轉移 ($p = 0.017$)、和淋巴管侵襲 ($p = 0.002$)。血清 CRP 的上升和病理較高進行期有很強的平行關係 ($p = 0.001$)。血清 CRP 高值者 (≥ 3.0 mg/L) 的和低值者 (< 3.0 mg/L) 相比較時，高值者之長期存活呈有意義的低下 (27.1% 比 54.1%，log rank $p = 0.0010$)。

結 論： 有 38.2% 胃癌病人手術前的血清會呈現升高的現象。CRP 高值和胃癌的擴展或進行期別有密切的關係，並且會有比較不好的存活結果。雖然血清 CRP 不是一種專屬胃癌特定的生物標記，它可做爲治療胃癌時一種具有潛能的預後指標，在未來也許會研發成一種治療的標靶。

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關鍵詞： C-反應性蛋白質，發炎性生物標記，預後因子，胃癌

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