Gastric Cancer (2020) 23:937–943
https://doi.org/10.1007/s10120-020-01073-5

ORIGINAL ARTICLE

Prognostic value of postoperative C-reactive protein elevation versus complication occurrence: a multicenter validation study

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Received: 23 January 2020 / Accepted: 6 April 2020 / Published online: 20 April 2020

Abstract

Background Several studies have shown that postoperative complications worsen the prognosis of patients with malignancies. However, our previous study showed that C-reactive protein (CRP) elevation over 12 mg/dL was a more reliable prognostic indicator than complication occurrence. This large-scale, multicenter validation study aimed to confirm the prognostic value of postoperative CRP elevation in resectable gastric cancer.

Methods Data of 1456 patients with pT2–T4 gastric cancer who underwent R0 resection were collected from 21 institutions. The prognostic value of the highest postoperative serum level of CRP (CRP_{max}) during hospitalization was evaluated using the Kaplan–Meier method. The prognostic independence of CRP_{max} with assessed with a Cox multivariate analysis of recurrence-free survival (RFS).

Results RFS in the high CRP_{max} (≥ 12 mg/dL) group was significantly worse than that in the low CRP_{max} (<12 mg/dL) group (log-rank $P=0.002$). The recurrence pattern showed that liver metastasis occurred more frequently in the high CRP_{max} group (9.2%) than in the low CRP_{max} group (4.7%) ($P=0.001$). In patients without intra-abdominal infectious complications, the high CRP_{max} group showed significantly worse RFS than the low CRP_{max} group (log-rank $P=0.026$). In patients with intra-abdominal infectious complications, the high CRP_{max} group had worse RFS than the low CRP_{max} group, but this difference was not significant (log-rank $P=0.075$). Cox multivariate analysis with 13 covariables showed that CRP_{max} ($P=0.043$) was an independent prognostic factor, but postoperative complications were not ($P=0.387$).

Conclusion Postoperative CRP elevation was a better predictor of prognosis in patients with gastric cancer than the occurrence of intra-abdominal infectious complications.

Keywords Gastric cancer · Gastrectomy · C-reactive protein · Postoperative complication

Introduction

Gastric cancer is a common malignancy worldwide [1]. While surgical resection is the most effective curative treatment, many patients still experience recurrence [2, 3]. Pathological TNM staging is the most useful indicator of prognosis after surgery [4], but it is still insufficient. We, therefore, need additional prognostic indicators to complement the TNM stage and to determine optimal postoperative strategies, including adjuvant treatment, in patients with resectable gastric cancer.

Several studies have shown that postoperative complications worsen the prognosis of patients with malignancies [5–8]. Such complications increase the levels of inflammatory cytokines such as interleukin-6 (IL-6) and may lead to the proliferation of residual cancer cells [9–11]. These

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outcomes can be caused by excessive surgical stress even if postoperative complications do not occur. Indeed, several randomized controlled trials demonstrated that compared with standard surgery, extended surgery worsened the prognosis of patients with gastroesophageal cancer [12–14]. C-reactive protein (CRP) is the most common indicator of systemic inflammation and is closely correlated with serum IL-6 levels [15, 16]. We previously showed that CRP elevation over 12 mg/dL was a more reliable indicator of worse recurrence-free survival (RFS) in gastric cancer patients than the occurrence of postoperative complications [17]. However, since the study was conducted at a single institution, we considered it important to validate the usefulness of CRP elevation in a large-scale multicenter study. Thus, we conducted this multicenter validation study to confirm the prognostic value of postoperative CRP elevation with over 1400 patients who underwent surgical resection of pT2–T4 gastric cancer.

Methods

Patients

The eligible population in this study consisted of patients with pathological T2 or greater advanced gastric cancer who underwent R0 resection between January 2008 and December 2010 at 21 institutions belonging to the Clinical Study Group of Osaka University. Exclusion criteria were as follows: synchronous coexisting cancer, metachronous cancer within 5 years, and preoperative treatment. TNM staging was performed according to the 7th edition of the Union for International Cancer Control (UICC) TNM classification [4]. In principle, gastrectomy, lymph node dissection, adjuvant chemotherapy, and postoperative follow-up were carried out according to the 3rd edition of the Japanese Gastric Cancer Treatment Guidelines [18]. This study was approved by the institutional review board of Osaka University Hospital (No. 15001).

Statistics

The primary endpoint of this study was the association between prognosis and the highest postoperative serum level of CRP (CRP_{max}) during the hospital stay. Statistical differences were also examined after adjustment for the presence or absence of postoperative complications. Postoperative complications were assessed according to the Clavien-Dindo classification [19, 20]. We defined postoperative complications as intra-abdominal infectious complications of Grade II or higher, in accordance with a similar study in the field of gastric cancer surgery [8].

Associations between clinicopathological factors and CRP_{max} were compared using the chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables. Recurrence-free survival (RFS) was defined as the time from surgery to either the first recurrence or death from any cause. Overall survival (OS) was defined as the time from surgery to death from any cause. RFS and OS curves were estimated using the Kaplan–Meier method, and survival differences were compared using the log-rank test. Cox proportional hazards models were used for both univariate and multivariate analyses. *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed with the SPSS statistical package, version 24.0 (SPSS, Chicago, IL, USA).

Results

Study population

A total of 1456 patients with pT2–T4 gastric cancer were enrolled in this study (Table 1). The median CRP_{max} levels were 11.75 mg/dL (range, 0.17–43.10 mg/dL) in the whole patients, 7.95 mg/dL (range, 0.17–11.96 mg/dL) in the low CRP_{max} group, and 17.49 mg/dL (range, 12.00–43.10 mg/dL) in the high CRP_{max} group. Male patients and patients with a high body mass index were more common in the high CRP_{max} (≥ 12 mg/dL) group than in the low CRP_{max} (< 12 mg/dL) group. The high CRP_{max} group included more patients with differentiated histological type, total gastrectomy, long operation time, large amount of intraoperative blood loss, and advanced pT tumors than the low CRP_{max} group. Postoperative complications occurred in 18 patients (2.4%) in the low CRP_{max} group and 159 patients (22.5%) in the high CRP_{max} group. The most frequent complications were anastomotic leakage in 74 patients (5.1%), abdominal abscess in 65 (4.5%), and pancreatic fistula in 59 (4.1%).

Kaplan–Meier survival analysis

At the median follow-up duration of 61.0 months for the censored cases, the RFS in the high CRP_{max} group was significantly worse than that in the low CRP_{max} group (log-rank $P = 0.002$) (Fig. 1a). The hazard ratio (HR) of recurrence in the high CRP_{max} group was 1.32 (95% CI, 1.11–1.56), and the 5-year RFS rates were 59.8% in the high CRP_{max} group and 67.1% in the low CRP_{max} group. The OS also showed a significant difference between the two groups (log-rank $P < 0.001$). The HR of death in the high CRP_{max} group was 1.43 (95% CI, 1.18–1.72), and the 5-year OS rates were 65.5% in the high CRP_{max} group and 74.6% in the low CRP_{max} group. In terms of recurrence pattern, only liver metastasis occurred significantly more frequently in the high

Table 1 Patient characteristics according to the peak serum CRP concentration (CRP_{max})

	Low CRP_{max} (< 12 mg/dL) ($n = 749$)	High CRP_{max} (≥ 12 mg/dL) ($n = 707$)	*P* value
Age (median, range), (years)	68 (24–94)	70 (26–92)	0.008
Sex			< 0.001
Male	439 (58.6%)	568 (80.3%)	
Female	310 (41.4%)	139 (19.7%)	
Body mass index (median, range), (kg/m^2)	21.5 (12.9–31.6)	22.9 (12.0–33.6)	< 0.001
Histological type			0.024
Differentiated	334 (44.6%)	357 (50.5%)	
Undifferentiated	415 (55.4%)	350 (49.5%)	
Approach			0.100
Open	645 (86.1%)	629 (89.0%)	
Laparoscopic	104 (13.9%)	78 (11.0%)	
Type of gastrectomy			< 0.001
Subtotal	518 (69.2%)	413 (58.4%)	
Total	231 (30.8%)	294 (41.6%)	
Lymphadenectomy			0.125
< D2	163 (21.8%)	131 (18.5%)	
≥ D2	586 (78.2%)	576 (81.5%)	
Operation time (median, range), (min)	223 (65–499)	249 (100–535)	< 0.001
Intraoperative blood loss (median, range), (mL)	250 (0–3500)	400 (0–6340)	< 0.001
pT status			0.013
T2	240 (32.0%)	177 (25.0%)	
T3	251 (33.5%)	263 (37.2%)	
T4	258 (34.4%)	267 (37.8%)	
pN status			0.304
N0	311 (41.5%)	264 (37.3%)	
N1	154 (20.6%)	142 (20.1%)	
N2	139 (18.6%)	149 (21.1%)	
N3	145 (19.4%)	152 (21.5%)	
Adjuvant chemotherapy			0.859
Absent	334 (44.6%)	312 (44.1%)	
Present	415 (55.4%)	395 (55.9%)	
Postoperative complications			< 0.001
Absent	731 (97.6%)	548 (77.5%)	
Present	18 (2.4%)	159 (22.5%)	

pT/N status and pStage were according to the Union for International Cancer Control (UICC) TNM classification of malignant tumours (7th edition). Postoperative complications mean only intra-abdominal infectious complications of Grade II or higher (Clavien-Dindo classification)

CRP_{max} group (9.2%) than in the low CRP_{max} group (4.7%) ($P = 0.001$) (Table 2). Even in the patients who did not have a recurrence in the liver, the high CRP_{max} group showed significantly worse RFS and OS than the low CRP_{max} group (log-rank $P = 0.044$, $P = 0.008$, respectively).

Similarly, the RFS was significantly worse in patients who had postoperative complications than in those who did not (log-rank $P = 0.016$) (Fig. 1b). We conducted a subgroup analysis to evaluate the prognostic value of postoperative CRP elevation independently of the presence or absence of postoperative complications. Among patients with no postoperative complications, the RFS was significantly worse in the high CRP_{max} group than in the low CRP_{max} group (log-rank $P = 0.026$; Fig. 2a). Among patients with postoperative complications, the high CRP_{max} group had worse RFS than the low CRP_{max} group, but this difference was not significant (log-rank $P = 0.075$; Fig. 2b).

Cox multivariate analysis

To assess the prognostic value of CRP_{max} independently of other confounding factors, we conducted a Cox multivariate

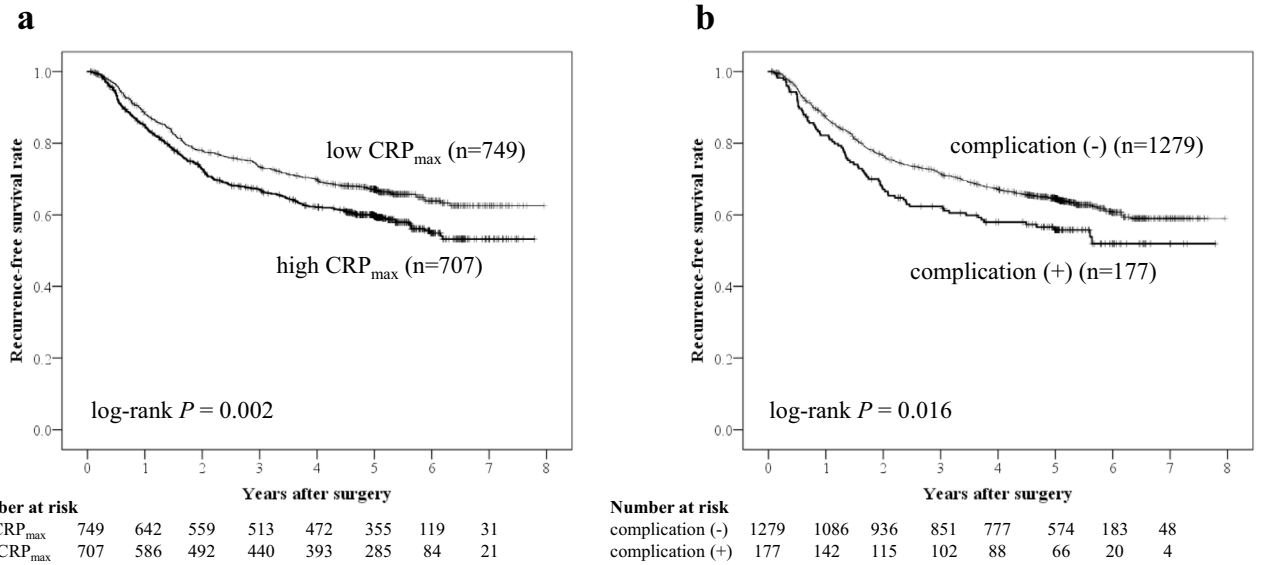

Fig. 1 Kaplan–Meier recurrence-free survival between the low (< 12 mg/dL) and high CRP_{max} (≥ 12 mg/dL) groups (**a**) and between patients without and with postoperative complications (**b**)

Table 2 Patterns of recurrence

Variable	Low CRP_{max} ($n=749$)	High CRP_{max} ($n=707$)	*P* value
Recurrence	196 (26.2%)	231 (32.7%)	0.006
Peritoneum	88 (11.7%)	79 (11.2%)	0.731
Liver	35 (4.7%)	65 (9.2%)	0.001
Lymph node	68 (9.1%)	59 (8.3%)	0.620
Local	5 (0.7%)	11 (1.6%)	0.104

analysis of RFS with 13 covariables (Table 3). The multivariate analysis identified CRP_{max} ($P=0.043$) as an independent prognostic factor, along with age ($P<0.001$), body mass index ($P=0.008$), type of gastrectomy ($P=0.006$), pT status ($P<0.001$), pN status ($P<0.001$), and adjuvant chemotherapy ($P=0.004$). By contrast, the postoperative complication was not a significant factor ($P=0.387$).

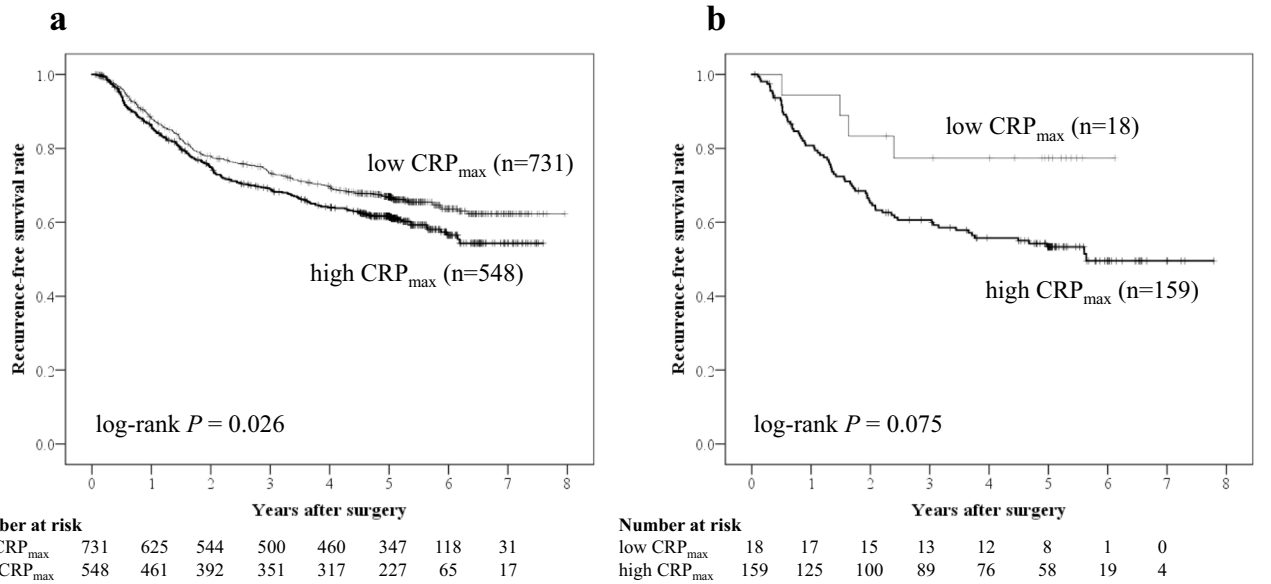

Fig. 2 Kaplan–Meier recurrence-free survival between the low (< 12 mg/dL) and high CRP_{max} (≥ 12 mg/dL) groups in patients without (**a**) and with (**b**) postoperative complications

Table 3 Cox multivariate analysis of prognostic factors associated with recurrence-free survival after gastric surgery

Variables	HR (95% CI)	*P* value
Age		
≥ 70 years	1.54 (1.28–1.86)	< 0.001
Sex		
Male	1.05 (0.86–1.29)	0.610
Body mass index		
< 22 kg/m^2	1.27 (1.06–1.52)	0.008
Histological type		
Differentiated	1.12 (0.94–1.34)	0.218
Approach		
Open	1.21 (0.87–1.67)	0.255
Type of gastrectomy		
Total	1.29 (1.07–1.54)	0.006
Lymph node dissection		
D2	1.19 (0.95–1.48)	0.127
Operation time		
≥ 240 min	1.05 (0.86–1.27)	0.631
Blood loss		
≥ 320 mL	1.01 (0.83–1.24)	0.913
pT status		
T4	2.05 (1.70–2.46)	< 0.001
pN status		
N1–N3	2.79 (2.20–3.53)	< 0.001
Adjuvant chemotherapy		
No	1.37 (1.11–1.70)	0.004
Postoperative complication		
Yes	1.12 (0.86–1.46)	0.387
CRP_{max}		
≥ 12 mg/dL	1.21 (1.01–1.47)	0.043

Discussion

This large-scale, multicenter study validated our initial finding that postoperative CRP elevation was an independent prognostic factor in patients who underwent surgical resection of pT2–T4 gastric cancer. The occurrence of postoperative complications was a significant prognostic factor in a univariate Kaplan–Meier analysis but not in a Cox multivariate analysis, indicating that CRP_{max} is a comprehensive prognostic indicator that takes into account the influence of postoperative complications. Moreover, in terms of objectivity, CRP_{max} has a higher prognostic value than complication occurrence.

Several previous studies in various fields of cancer surgery showed that the occurrence of postoperative complications worsened patient prognosis [5–8]. Salvans et al. reported that postoperative peritoneal fluid obtained from patients with an anastomotic leak or intra-abdominal abscess enhanced both cell migration and cell invasion capacities in in vitro assays [9]. They concluded that intra-abdominal infectious complications enhance the invasiveness of residual tumor cells after surgery, leading to recurrence. Increased proinflammatory mediators such as interleukin-6 (IL-6) may play an important role in promoting proliferation and migration of residual cancer cells [21, 22]. Kubota et al. reported that postoperative complications of Grade II or higher were a significant prognostic indicator in pStage II and III but not pStage I gastric cancer [23]. However, their study was retrospectively conducted at a single institution, and more than half of their patients had early (pT1) gastric cancer. By contrast, in this study we enrolled a much larger number of patients with advanced (pT2–T4) gastric cancer. Our multivariate analysis revealed that the occurrence of postoperative complications was not an independent prognostic indicator, and that instead it was a confounding factor for CRP elevation.

CRP elevation is a comprehensive indicator of postoperative inflammation status, which in turn reflects the levels of inflammatory cytokines such as IL-6 [15, 16]. Even if postoperative complications do not occur, excessive surgical stress can result in the production of inflammatory cytokines, which leads to the promotion of adhesion of circulating tumor cells to the vascular endothelium of distant organs by enhancing the E-selectin expression [24–27]. This mechanism may explain the reason why liver not peritoneal metastasis occurred significantly more frequently in the high CRP_{max} group in our study. Extended surgery that causes excessive surgical stress may worsen both patient prognosis and quality of life. Thus, minimally invasive surgery that does not increase the occurrence of postoperative complications is ideal in patients with cancer.

Recently, several complex prognostic indicators have been reported, including CRP. The Glasgow prognostic score, which uses CRP and albumin, is a well-known prognostic marker in various kinds of cancer surgeries [28]. The CRP/albumin ratio (CAR) was also reported to be a useful prognostic marker in hepatocellular carcinoma [29]. However, most studies using these complex indicators or CRP alone examined only the prognostic value of the preoperative CRP level [28–31]. Preoperative CRP mainly reflects oncological status, whereas postoperative CRP reflects both oncological status and the inflammatory response after surgery, and may, therefore, be more useful for predicting patient prognosis [32]. A large-scale study comparing the prognostic values of postoperative CRP alone with complex indicators that include postoperative CRP is warranted in the future.

This study has several limitations. First, it was a retrospective study and was therefore prone to selection bias, although the number of patients was very large. To reduce bias as much as possible, we collected the data of consecutive patients who underwent R0 resection between January

2008 and December 2010 at 21 institutions. Second, no consensus guidelines currently exist for determining the type of complications that affect prognosis. However, a meta-analysis showed the relationship between complications and reduced survival was stronger when only infectious complications were considered as compared with all complications [32]. In this study, we, therefore, assessed intra-abdominal infectious complications in accordance with a previous study in gastric cancer surgery [8]. Third, the days of routine CRP examination were not fixed in this study, and we used the highest postoperative serum level of CRP during the hospital stay as a representative value of postoperative CRP elevation. However, CRP level at the fixed date after surgery may be better considering the simplicity. Indeed, Watt et al. examined the prognostic values of CRP and albumin levels on days 3 or 4 after colorectal surgery [33]. We actually confirmed that most of the participating institutions routinely examined CRP levels either on days 2–4. We hope future studies will evaluate which is a better prognostic indicator CRP_{max} or CRP level at the fixed date.

In conclusion, postoperative CRP elevation was a much more effective predictor of prognosis in patients with gastric cancer than the occurrence of intra-abdominal infectious complications. CRP_{max} over 12 mg/dL may be a useful complement to the TNM stage in determining the indications for adjuvant treatment to improve the prognosis of gastric cancer patients more. Surgeons should ideally avoid increasing postoperative CRP levels by reducing excessive surgical stress and postoperative complications.

Funding The authors declare that this study was not funded.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Consent to participate was not considered necessarily.

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