RESEARCH ARTICLE

Prognostic Role of C-reactive Protein in Gastric Cancer: A Meta-analysis

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Abstract

Background: A number of studies have investigated the association between increased pretreatment serum C-reactive protein (CRP) levels and the prognosis of gastric cancer. However, due to the inconsistent results, whether the serum CRP level can be a prognostic factor in primary gastric cancer remains controversial. Methods: We searched Medline, PubMed, Embase and the Cochrane Central Register of Controlled Trials for relevant high-quality reports. A meta-analysis was carried out using the included studies to assess the association between pretreatment serum CRP level and overall survival (OS) in patients with gastric cancer. Correlation analyses were conducted to evaluate the relationship between serum CRP and tumor characteristics such as tumor node metastasis (TNM) stage and recurrence. Results: Twelve reports involving 2,597 patients with gastric cancer were included. Primary meta-analysis indicated a significant association between elevated CRP level and poor OS (HR 1.77, 95% CI 1.56-2.00). Subgroup analyses showed no single factor could alter the primary results when we divided the included studies by "number of patients", "max follow-up period", "TNM stage", "treatment" and "cut-off value". Correlation analyses showed that serum CRP level was significantly related to TNM stage (OR 2.96, 95% CI 2.22-3.93) and tumor recurrence (OR 1.81, 95% CI 1.21-2.71). Conclusions: We demonstrated that increased pretreatment serum CRP level (≥10mg/L) was significantly associated with poor prognosis in gastric cancer patients, either in early or advanced stages.

Keywords: C-reactive protein - gastric carcinoma - prognosis - meta-analysis

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Introduction

Despite of the decreased incidence in past years, gastric cancer has continued to be a great threat to human life, especially in Asia. In China, it is the second most common cancer and the third most common reason of death in cancer patients (Chen et al., 2013). Similarly, situations are hardly optimistic in Japan and Korea, where the morbidity and mortality remain a major problem (Jemal et al., 2011). At present, complete resection is the only curative therapy, with evidence for increased survival with the addition of adjuvant therapies (40% 5-year survival) (Macdonald et al., 2001; Cunningham et al., 2006; Sakuramoto et al., 2007). However, in China only 10% of the patients are diagnosed at an early stage, while 90% of the patients are diagnosed at an advanced stage when the tumor is inoperable (Zheng et al., 2013). For these unfortunate people with advanced gastric cancer, the 5-year survival rate is less than 10% (Zheng et al., 2013). Nowadays Tumor Node Metastasis (TNM) staging remains to be the major tool for prognosis evaluation in gastric cancer before treatment. However the accuracy of TNM staging is far from satisfactory due to the individual differences. It is somewhat common that in the same stage, patients have different outcomes. This brings great difficulty to individualized treatment. Thus there is an urgent need for us to find another biomarker to give additional information on the prognosis before treatment.

C-reactive protein (CRP), named for its capacity to precipitate C-polysaccharide of Streptococcus pneumonia (Tillett et al., 1930), has been widely known as a protein involved in host defense and accepted to be a sensitive but nonspecific systemic marker of inflammation. Mainly produced by hepatocytes (Hurlimann et al., 1966), CRP in plasma elevates during acute inflammation caused by infection and other stimuli such as trauma burns (Gabay et al., 1999). Recently, as a marker of inflammation, the prognostic value of CRP in cancer has also been uncovered. A study included 199 patients with unresectable pancreatic cancer showed the elevated CRP concentration was independently associated with overall survival (OS) (p=0.027) (Pine et al., 2009). And Karakiewicz (Karakiewicz et al., 2007) found that CRP was a predictor of renal cell cancer-specific mortality (p=0.003). Similar results were also found in gastric cancer. Shimura et al. (2012) found that progression-free

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Table 1. Newcastle - Ottawa Quality Assessment Scale

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average gastric cancer patients in the community
b) somewhat representative of the average gastric cancer patients in the community
c) selected group of users (e.g. nurses, volunteers)
d) no description of the derivation of the cohort
2) Selection of the non-exposed cohort
a) drawn from the same community as the exposed cohort
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
a) secure record (e.g. surgical records)
b) structured interview
c) written self-report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes
b) no
Comparability
Comparability of cohorts on the basis of the design or analysis
a) study controls for metastasis or recurrence
b) study controls for any additional factor (age, gender, TNM stage, etc.)
Outcome
1) Assessment of outcome
a) independent blind assessment
b) record linkage
c) self-report
d) no description
2) Was follow-up long enough for outcomes to occur (Death)
a) yes (3 years)
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for
b) subjects lost to follow up unlikely to introduce bias - small number lost - > 25% follow up, or description provided of those lost)
c) follow up rate < 75% (select an adequate %) and no description of those lost
d) no statement

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

survival (PFS) was significantly shorter in the high-CRP level patients with gastric cancer. Nozoe et al. (2011) investigated 204 patients who underwent curative resection of gastric cancer and he found that the patients with preoperative CRP elevation had significantly poorer survival (p<0.0001). However, there were also opposite views. Aizawa et al. (2011) argued that CRP was not an independent prognostic factor for gastric cancer patients in stage I-III (p=0.072). And Fujitani et al. (2011) report that raised CRP level was not prognostically significant in gastric cancer patient in stage I-IV (p=0.497). Due to the inconsistent results, the prognostic value of CRP in gastric cancer remains unsure. We thus conducted this meta-analysis to assess the association between pretreatment serum CRP level and the OS of patients with gastric cancer.

Materials and Methods

Searching strategy

We searched the Cochrane Central Register of Controlled Trials, Medline, PubMed, and Embase to identify studies that assessed the prognostic value of CRP for primary gastric cancer. The search strategies included the keywords variably combined by "c-reactive protein", "CRP", "prognosis", "prognostic", "gastric", "carcinoma" or "cancer".

Study inclusion/exclusion criteria

Studies were included if they met all of the following inclusion criteria: (i) patients were pathologically diagnosed as gastric cancer; (ii) the level of serum CRP were measured before treatment; (iii) the relationship between the OS of gastric cancer patients and the serum CRP level was reported; (iv) they were published as a full paper in English. Study was excluded based on any of the following criteria: (i) it was a review, letter or experiment on animal models; (ii) it lacked sufficient data to extract the hazard ratios (HRs) and the 95% confidence intervals (CIs).

Study quantity assessment

To evaluate the study quality, three investigators (Yu, Zhang and Wang) read each study independently and scored them using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2008) (Table 1). This scale is an eight-item instrument that allows for assessment of the quality of nonrandomized studies for meta-analyses. Interpretation of the scale is performed by a "star system" in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for cohort studies respectively.

Data extraction

Two investigators (Yu and Zhang) reviewed the included reports and extracted the data independently. Disagreements were resolved by discussion. If the results reported in included studies have possible overlap (e.g., same authors, institutions), only the most recent or the most complete study was involved in the analysis. The extracted data included "authors", "sample size", "publication year", "country", "median age", "TNM stage", "treatment information", "recurrence information", "cut-off level", and HRs and their 95% CIs for the correlation between CRP level and OS. If the HRs and 95% CIs were not directly reported, we made mathematical estimations according to the methods developed by Parmar et al. (1998).

Statistical analysis

Pooled HRs and their 95% CIs were used to estimate the effect of CRP level on OS, while pooled odds ratios (ORs) and their 95% CIs were used to estimate the correlation between CRP and TNM stage or tumor recurrence. A significant heterogeneity was defined as P<0.10 or I^2>50% (Higgins et al., 2003). An observed HR>1 indicated a worse outcome for the increased-CRP group compared to the normal-CRP group and it was considered statistically significant if the 95%CI did not overlap 1. Subgroup analyses were done by stratifying the included studies by "number of patients", "max follow-up period", "TNM stage", "treatment" and "cut-off value". In addition, publication bias was evaluated by both the Begg's funnel plot and Egger's bias indicator test (Begg et al., 1994; Egger et al., 1997). All statistical calculations were performed using Stata version 12.0.

Results

Searching results

According to the searching strategies, a total of 86 studies were identified. After a series of screening based

Table 2. Characteristics of Included Studies

Author	Year	Sample size	Gender (M/F)	Median age (years)	Median follow-up period (months)	TNM stage of included patients	Treatment	Country	Hazard ratios	Cut-off level	Study quality points
Shimura et al.	2012	61	43/18	N/A	N/A	IV	Multiple therapies	Japan	Reported in text	≥10.0mg/L	7
Wang et al.	2012	324	225/99	N/A	39.9 (23.77-57.43)	III	Radical surgery	China	Reported in text	≥10.0mg/L	8
Jeong et al.	2012	104	69/35	52.5 (28-82)	11.9(10.2-13.5)	IV	NS	Korea	Reported in text	≥10.0mg/L	6
Kwon et al.	2012	115	68/47	59 (24-75)	66.6(9.3-88.8)	I-IV	Multiple therapies	Korea	Estimated	≥100mg/L	7
Hwang et al.	2011	402	203/199	59 (19-80)	11.4(1.1-58.5)	IV	NS	Korea	Reported in text	≥10.0mg/L	8
Aizawa et al.	2011	262	180/82	64	54.5	I-III	Radical surgery	Japan	Estimated	≥10.0mg/L	7
Nozoe et al.	2011	204	142/62	67 (27-89)	(2-109)	I-III	Radical surgery	Japan	Estimated	≥5.0mg/L	7
Iwasa et al.	2011	79	43/36	58 (20-77)	3.3(0.4-29.7)	IV	NS	Japan	Reported in text	≥20.0mg/L	6
Chang et al.	2010	170	112/58	65.1 (29-89)	76.8 (39-113)	I-IV	Multiple therapies	Taiwan	Estimated	≥3.0mg/L	7
Mohri et al.	2010	357	245/112	63.4 (32-87)	68 (1-70)	I-III	Radical surgery	Japan	Reported in text	≥3.0mg/L	7
Fujitani et al.	2011	53	37/16	62 (33-86)	N/A	I-IV	Multiple therapies	Japan	Reported in text	≥3.0mg/L	7
Hashimoto et al.	2010	466	305/161	60 (22-73)	N/A	I-IV	Multiple therapies	Japan	Reported in text	≥10.0mg/L	7

M/F, male/female; Treatment describes the therapies taken among the patients involved in each study. NS, non-surgical therapy; Multiple therapies, including surgical resection and non-surgical therapies such as chemotherapy or radiotherapy. Study quality points is listed using the results of the Newcastle-Ottawa quality assessment scale (Table 1). N/A, not available

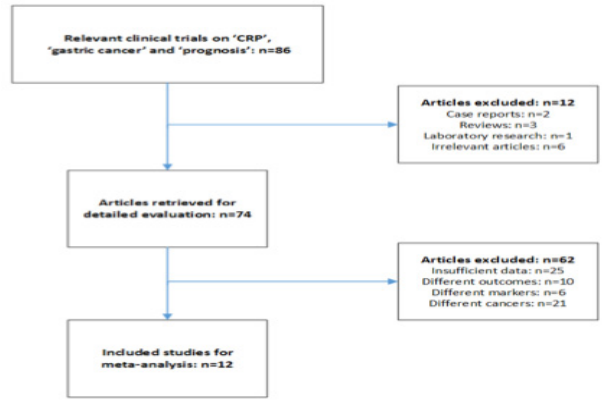

Figure 1. Flow Chart of the Meta-analysis

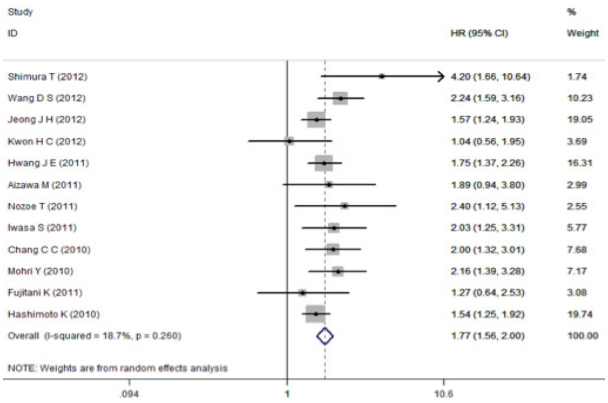

Figure 2. Forest Plot of the Association Between Elevated CRP and Poor OS in Gastric Cancer

on the inclusion/exclusion criteria mentioned above, 12 studies were eventually eligible for the meta-analysis. The searching results were shown in Figure 1.

The 12 studies included a total of 2597 patients, with 1672 males (64.4%) and 925 females (35.6%). The sample size of each study ranged from 53 to 466 patients (mean 204). All the studies were performed in Asia, 7 from Japan, 3 from Korea and 2 from China. The quality scores ranged from 6 to 8 (mean score 7). The basic characteristics of the included studies were listed in Table 2.

Primary analyses

The results of primary pooled statistics indicated a significant association between elevated CRP and poor OS (HR 1.77, 95% CI 1.56-2.00). No significant heterogeneity was observed in primary analysis (I^2=18.7%, p=0.260) (Figure 2).

Table 3. Subgroup Analyses of Pooled Hazard Ratio (HR) for Increased Serum C-reactive Protein (CRP) and Overall Survival (OS) in Gastric Cancer

Subgroup	Number of cohorts	Number of patients	HR (95% CI)	*P* value	Heterogeneity I^2(%)	Heterogeneity *P* value
Number of patients						
>200	6	2015	1.79 (1.56, 2.04)	0	0	0.433
≤200	6	582	1.67 (1.41, 1.97)	0	39.5	0.142
Max follow-up						
>5years	4	846	1.85 (1.35, 2.54)	0	30.9	0.227
≤5years	4	909	1.77 (1.53, 2.06)	0	6.7	0.359
TNM stage						
IV	4	646	1.79 (1.44, 2.23)	0	35.7	0.198
I-III	4	1147	2.19 (1.72, 2.77)	0	0	0.97
Treatment						
Radical surgery	4	1147	2.19 (1.72, 2.77)	0	0	0.97
Non-surgical therapy	3	1450	1.68 (1.44, 1.97)	0	0	0.594
Cut-off value						
≥10mg/L	6	1619	1.71 (1.51, 1.92)	0	33.6	0.184
≥3mg/L	3	580	1.92 (1.46, 2.52)	0	0	0.26

HR, hazard ratio; CI, confidence interval; TNM, tumor node metastasis

Subgroup Analyses

We also performed subgroup analyses by dividing the studies based on "number of patients", "max follow-up period", "TNM stage", "treatment" and "cut-off value".

When stratified by "number of patients", the ">200" group yielded a HR of 1.79, and the 95% CI was 1.56-2.04. The "≤200" group yielded a HR of 1.67, and the 95% CI was 1.41-1.97.

When stratified by "max follow-up period", the ">5years" group yielded a HR of 1.85, and the 95% CI was 1.35-2.54. The "≤5years" group yielded a HR of 1.77, and the 95% CI was 1.52-2.06.

When stratified by "TNM stage", the "Stage IV" group yielded a HR of 1.79, and the 95% CI was 1.44-2.23. The "Stage I-III" group yielded a HR of 2.19, and the 95% CI was 1.72-2.77.

When stratified by "treatment", the "Radical surgery" group yielded a HR of 2.19, and the 95% CI was 1.72-2.77. The "Non-surgical therapy" group yielded a HR of 1.68, and the 95% CI was 1.44-1.97.

When stratified by "cut-off value", the "≥10mg/L" group yielded a HR of 1.71, and the 95% CI was 1.52-1.92. The "≥3mg/L" group yielded a HR of 1.92, and the 95% CI was 1.46-2.52.

All the results of subgroup analyses were showed in Table 3.

Table 4. Correlation analyses on increased serum CRP and TNM stage, tumor recurrence in gastric cancer

Stratification	Number of cohorts	Number of patients	References	OR (95% CI)	P value	Heterogeneity	
						I^2(%)	*P* value
TNM stage (II/III vs I)	2	1425	16,29	2.96 (2.22, 3.93)	0	12.2	0.286
Recurrence	2	1282	13,29	1.81 (1.21, 2.71)	0.004	25.3	0.247

OR, odds ratio; CI, confidence interval; TNM, tumor node metastasis

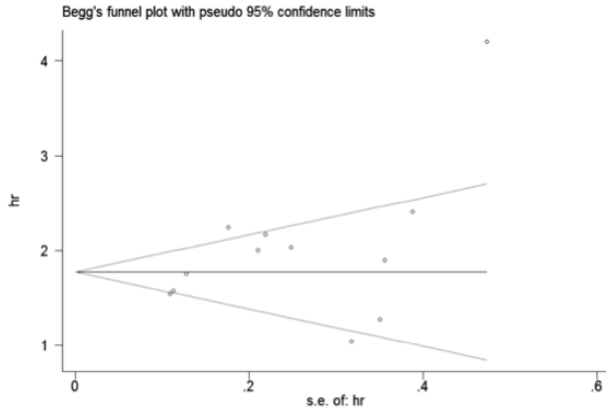

Figure 3. Begg's Funnel Plot for the Visual Assessment of Publication Bias for the Included Studies

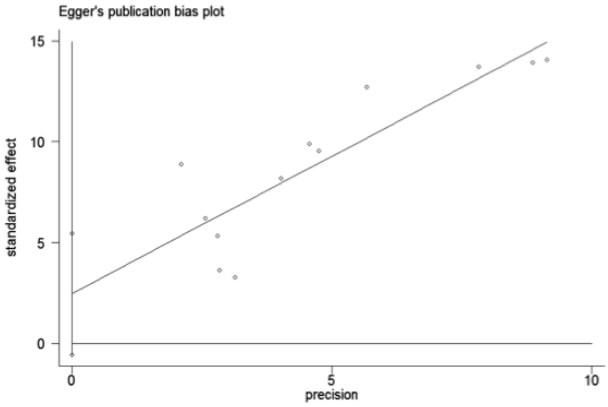

Figure 4. Egger's Publication Bias Plot

Correlation analyses

Two studies (Nozoe et al., 2011; Woo et al., 2012) provided the numbers of patients in stage I-II and stage III separately, as well as the numbers of patients who had an elevation of CRP level in each stage. We use these data to assess the correlation between serum CRP level and TNM stage. It should be noted that we included Woo's study (Woo et al., 2012) which was excluded previously because no data on OS was reported. As a result, the combined OR was 2.96 (95% CI 2.22-3.93 p=0.000) with no significant heterogeneity (I^2=12.2%, p=0.286).

By the same method, we assessed the correlation between serum CRP level and tumor recurrence using the data from two studies (Shimura et al., 2012; Woo et al., 2012). The combined OR was 1.81 (95% CI 1.21-2.71 p=0.004) with no significant heterogeneity (I^2 = 25.3%, p=0.247) (Table 4).

Publication bias

We took Begg's and Egger's test on the 12 included studies. The p value indicated that no significant publication bias was observed (Begg's test: p=0.150, Egger's test: p=0.099) (Figure 3 and Figure 4).

Discussion

An effective pretreatment prognostic marker cannot only give information for prediction of survival, but more importantly, can help clinicians make decisions on treatment selection. An appropriate decision may result in better survival or better quality of life for patients. At present, the TNM staging remains the most common and effective way to predict the prognosis of gastric cancer before treatment (Mohri et al., 2010). However, most patients have developed advanced tumor or metastasis at the time of diagnosis, and the prognoses of patients in the same stage are often poles apart. Therefore the TNM staging alone cannot always make accurate predictions. We thus need to add other prognostic marker to provide more information on prognoses of gastric cancer patients.

In this meta-analysis, preliminary combined HRs showed that the increased CRP level in gastric cancer patients indicated a significant association with poor OS (HR 1.77, 95% CI 1.56-2.00). Although no heterogeneity was observed (I^2=18.7%, p=0.260), we did further subgroup analyses to ensure the homogeneity among the included studies.

We divided the included studies by "number of patients", "max follow-up period", "TNM stage", "treatment" and "cut-off value". Eventually, no alteration on heterogeneity was observed. However, we have to mention that the statistical results on heterogeneity cannot fully reflect the clinical heterogeneity. In our study, we have to consider "TNM stage" as one of the possible source of heterogeneity as the patients in stage IV differ greatly from those in earlier stage: (1) Unlike the patients in earlier stage, gastric cancer patients in stage IV with distant metastasis have lost the opportunity for operation and mostly have to receive palliative therapies (Catalano et al., 2009) and the difference in treatment contributes greatly to the different outcomes; (2) The patients in stage IV are usually in poor physical condition, suffering weight loss, vomiting, poor oral intake caused by gastrointestinal (GI) obstruction, and the eventually cachexia, while patients in earlier stage usually experience less complications and have better nutritional status (Gencer et al., 2009); (3) Tumors with distant metastasis have already undergone a series of changes in a molecular biological level, triggered a sequence of discrete steps such as so-called invasion-metastasis cascade (Talmadge et al., 2010), showing more malignant biological behavior, which results in the clinical heterogeneity between patients in stage IV and earlier stage. Besides the "TNM stage", "max follow-up period" is also considered another potential source of heterogeneity. The length of follow-up period influences the observation on therapeutic effect,

treatment-induced complications, tumor progression, metastasis and recurrence. Studies with longer follow-up period can yield different results in outcomes compared to those with shorter follow-up period. For example, in a phase 3 randomized trial, no evidence was found that the cetuximab-induced rash had any influence on OS for the patients with head and neck squamous-cell cancer at 3 years (Bonner et al., 2006). But at the 5th year, when they updated the survival data with prolonged follow-up period, they found that the OS was significantly improved in patients who experienced a cetuximab-induced rash compared to those with no rash (Bonner et al., 2010).

After the subgroup analyses, we also found that, when stratified by TNM stage, both subgroup (stage IV and stage I-III) showed significant HRs and 95% CIs (stage IV: 1.79, 95% CI 1.44-2.23, I^2=35.7%; stage I-III: 2.19, 95% CI 1.72-2.77, I^2=0). This result, on the other hand, indicated that no matter what stage the patients are in, the increased serum CRP level can significantly predict the poor survival.

In addition, when stratified by cut-off value, the results were also consistent no matter using 10mg/L (HR 1.71, 95% CI 1.51-1.92, I^2=33.6%) or 3mg/L (HR 1.92, 95% CI 1.46-2.52, I^2=0) as the cut-off value. Considering that most of the studies used 10mg/L, we recommended 10mg/L to be the first choice when using CRP to predict prognosis for gastric cancer patients.

What's more, our further analyses showed that increased pretreatment serum CRP significantly related to advanced tumor stage (OR 2.96, 95% CI 2.22-3.93) and tumor recurrence (OR 1.81, 95% CI 1.21-2.71), as was expected, which again indicated that increased serum CRP is a predictor of poor prognosis in gastric cancer.

The underlying molecular mechanism of the prognostic value of CRP in gastric cancer remains unclear. According to the recent studies, the close association between systemic inflammation and cancer can be the major factor. On the one hand, long-term inflammation can lead to tumorigenesis. A typical example is the relation between Helicobacter pylori infection and gastric cancer (Parsonnet et al., 1991). H. pylori infection can induce acute or chronic gastritis, which may lead to gastric cancer after the gastric mucosa passing through a sequence of histological changes, including atrophy, intestinal metaplasia, dysplasia, and adenocarcinoma (Correa, 1992). The local infection induces a series of cytokines (IL-1 β , IL-2, IL-6, IL-8, IL-23 and IL-17 and TNF- α , etc.) released from either immune or non-immune cells (Caruso et al., 2007), and these cytokines enhance the production of CRP from hepatocytes. A meta-analysis of 12 prospective cohorts demonstrated that H. pylori seropositivity was strongly associated with the progression of gastric cancer (Forman, 2001). On the other hand, with the progression of cancer, the tumor itself can also trigger regional inflammatory response and release pro-inflammatory cytokines, which results in the formation of an inflammatory microenvironment (Balkwill et al., 2001; Coussens et al., 2002; Mantovani et al., 2008). Several studies pointed out that the elevated inflammatory response was associated with poor local immune response to the tumor and contributed to the lymph node spread and metastasis through a series of steps, including recruitment of the regulatory T lymphocytes and chemokine, activation of cytokines interleukin-6 and tumor necrosis factor-alpha, induction of neutrophilia, and secretion of CRP (Ulich et al., 1987; Ulich et al., 1989; Heikkila et al., 2007; Crumley et al., 2010).

Interestingly, some recent studies suggested that Glasgow prognostic score (GPS) was an independent prognostic marker for gastric cancer patients (Hwang et al., 2011; Wang et al., 2012; Jeong et al., 2012). GPS is a combination of serum CRP and albumin concentrations (Forrest et al., 2003), which appears to reflect the systemic inflammatory response as well as nutritional status (Kao et al., 2010; Proctor et al., 2011). Nevertheless, in Hwang's study, where 402 patients with advanced gastric adenocarcinoma were included, poor GPS depended largely on elevated CRP level other than descending albumin level (Hwang et al., 2011). In another study, Crumley et al. (2006) indicated that low albumin was a confounding factor in the GPS scoring system. And Crumley also demonstrated that the development of hypo-albuminemia was secondary to an ongoing systemic inflammatory response and poor cancer specific survival was secondary to the systemic inflammatory response in patients with gastric cancer (Crumley et al., 2010). These results, from another perspective, showed that CRP is an effective marker to predict the prognosis for gastric cancer patients.

In addition, some limitations should be recognized in this meta-analysis. We have to admit that the number of included articles was limited due to the lack of relevant high-quality studies. Moreover, also because of the lack of relevant prospective study, most of the included studies were retrospective. More large-scale, high-quality and prospective studies are therefore needed to update our assessment and to give more convincing evidence in the future.

In conclusion, our meta-analysis showed that increased pretreatment serum CRP level were significantly associated with poor prognosis in gastric cancer patients, either in early stage or advanced stage. As a common serum protein that can be detected in a simple, inexpensive and invasive way, pretreatment serum CRP is considered to be a promising prognostic factor for gastric cancer patients. We suggest that serum CRP level and TNM stage can be used together before treatments to provide more appropriate prediction on survival and more reliable and effective information on treatment-decision for the patients with gastric cancer.

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The author(s) declare that they have no competing interests.

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