

Review Article

High Expression of C-reactive Protein Increases the Risk of Poor Prognosis in Patients with Gastric Cancer: A Meta-analysis

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Abstract: There are many researches on the correlation between C-reactive protein (CRP) and prognosis of gastric cancer, but whether CRP could be used as an evaluation indicator for prognosis of gastric cancer patients, which was still controversial. Therefore, we conducted meta-analysis based on 18 studies involving 3656 objects. The results show that, CRP was significantly correlated with the risk of poor prognosis of gastric cancer patients [HR (95% CI) 1.50 (1.24, 1.81) $P=0.000$], and the risk of the poor prognosis can be significantly increased when $CRP>10mg/L$. In the different clinical stage, high expression of CRP can increase the risk of poor prognosis. The CRP can be used as an important indicator of poor prognosis of gastric cancer patients.

Keywords: C-reactive Protein, Gastric Cancer, Prognosis, Meta-analysis

1. Introduction

Gastric cancer is one of the most common malignant tumors in humans, which ranks the fourth highest malignant tumor in the world, and the associated mortality rate takes the second place [1]. Morbidity and mortality of gastric cancer are the highest and increasing year by year in China [2]. The treatment of gastric cancer currently includes surgical resection, chemotherapy, radiotherapy, and other comprehensive treatment measures, but the prognosis is still poor, and the overall 5-year survival rate usually does not exceed 20% [3].

In tumor tissue, cells are present in the microenvironment

similar to chronic inflammation. Persistent inflammatory reactions occur in the microenvironment, which produces inflammatory media and continues to aggravate the inflammatory state of the tumor microenvironment. Moreover, cancer infiltration induces local tissue destruction, interferes with tissue homeostasis, and leads to systemic inflammatory reactions. Systemic inflammatory reaction has positive feedback with cancer invasion and metastasis. Abdominal metastasis of gastric cancer leads to abdominal cavity adhesion and obstruction of blood vessels, intestine and bile ducts, which aggravates systemic inflammation reactions [4].

C-reactive protein (CRP) is an acute phase protein

synthesized by hepatocytes, which increases in inflammatory diseases. Later studies show that the elevated levels of CRP are associated with an increased risk of colon cancer, lung cancer, prostate cancer and ovarian cancer [5]. Baba *et al* [6] found that CRP is a risk factor for poor prognosis of gastric cancer stage IV. However, some studies do not support this association. Aizawa *et al* [7] believed the CRP is not an independent risk factor for prognosis of gastric cancer patients in stage I-III ($P=0.072$). Fujitani *et al* [8] found there is no correlation between CRP and poor prognosis of gastric cancer patients ($P=0.497$). Therefore, in here we evaluate the relationship between CRP and risk of poor prognosis of gastric cancer patients by a comprehensive meta-analysis, so as to search for an important indicator of poor prognosis of gastric cancer patients.

2. Methods

2.1. Search Strategy

The literature search process is shown in Figure 1. Two investigators (Qian-Long Zhao and Jun-Yi Chen) independently searched the literature using PubMed, Embase, The Cochrane Library, Chinese Biomedical Literature Database (CBM), China Knowledge Resource Integrated Database (CNKI), VIP Database, and WanFang Database, from their inception to February 10th 2018. Search terms included “C-reactive protein” “C reactive protein” “CRP” “stomach neoplasms” “gastrectomy” “gastrointestinal cancer” “gastrointestinal malignancies”. These literature included full articles, review articles and meta-analyses in this area, which were searched for citations of further relevant published and unpublished research.

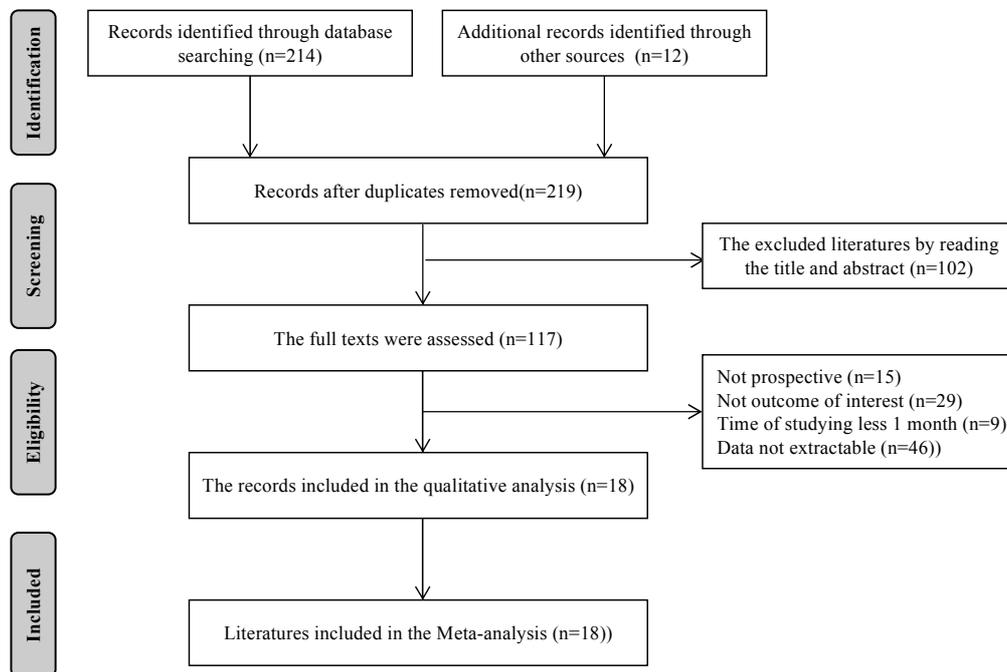


Figure 1. Flow diagram of the studies included and excluded in the Meta-analysis.

2.2. Inclusion and Exclusion Criteria

Literature met the following requirements were included: 1) patients were diagnosed clinically with gastric cancer; 2) the study was designed as a cohort study; 3) the report of the study should provide correlation between the CRP levels and the hazard ratio (*HR*) or the relative risk (*RR*) of the prognosis of gastric cancer patients. Or the raw data provided can be used to calculate the *HR*. In addition, Repeated report

should be excluded. The latest report would be included if the same cohort study repeated many times at different time points.

Exclusion criteria were as follows: 1) animal studies; 2) literature review summary; 3) the follow-up time is less than 1 month; 4) literature were not provided data on survival prognosis; 5) research and design have defects with incomplete data.

Table 1. Characteristics of included studies.

Study	Year	Sample size	Gender (M/F)	Age	Follow-up (months)
Albanopoulos et al	2013	177	75/102	38.1 (18-61)	1
Baba et al	2013	123	91/32	69 (26-88)	60
Chang et al	2010	170	112/58	65.1 (29-89)	76.8
Jeong et al	2012	104	69/35	52.5 (28-82)	11.9
Mohri et al	2010	357	245/112	63.4 (32-87)	68
Aizawa et al	2011	262	180/82	64	54.5
Nozoe et al	2011	204	142/62	67 (27-89)	60

Study	Year	Sample size	Gender (M/F)	Age	Follow-up (months)
Hashimoto et al	2010	466	305/161	60 (22-73)	6
Ishino et al	2014	214	137/77	NA	45
Fujitani et al	2011	53	37/16	62 (33-86)	39
Saito et al	2015	305	213/92	66 (30-92)	120
Shimure et al	2012	61	43/18	67 (32-79)	33
Iwasa et al	2011	79	43/36	58 (20-77)	3.3
Wang et al	2012	324	225/99	NA	39.9
Hwang et al	2011	402	203/199	59 (19-80)	11.4
Kwon et al	2012	115	68/47	59 (24-75)	66.6
Zhang et al	2015	150	93/57	32-83	10.6
Zhu et al	2016	90	49/41	23-79	10.5

Table 1. Continued.

Study	TNM	Treatment method	Country	Cut-off level (CRP)	Quality assessment
Albanopoulos et al	IV	Reduction surgery	Greece	5	7
Baba et al	IV	Reduction surgery	Japan	17	7
Chang et al	I-IV	Multiple therapies	China	3	7
Jeong et al	IV	NS	Korea	10	6
Mohri et al	I-III	Radical surgery	Japan	3	7
Aizawa et al	I-III	Radical surgery	Japan	10	7
Nozoe et al	I-III	Radical surgery	Japan	5	7
Hashimoto et al	I-IV	Reduction surgery	Japan	10	7
Ishino et al	I-III	Reduction surgery	Japan	5	7
Fujitani et al	I-IV	Multiple therapies	Japan	3	7
Saito et al	IV	surgery	Japan	120	7
Shimure et al	IV	Chemical therapy	Japan	10	7
Iwasa et al	IV	NS	Japan	20	6
Wang et al	III	Radical surgery	China	10	8
Hwang et al	IV	NS	Korea	10	8
Kwon et al	I-IV	Multiple therapies	Korea	10	7
Zhang et al	III-IV	Chemical therapy	China	10	7
Zhu et al	III-IV	Radical surgery	China	10	7

+ NA: Not available; NOS: The quality score by Newcastle-Ottawa Scale; RS: Reduction surgery; Mt: Multiple therapies; NS: Non-surgery; Ct: Chemical therapy.

2.3. Data Extraction

After removing the duplicates, two investigators (Fu-Lun Li and Ke Liu) independently screened the title and abstracts of all records, and then selected the articles that fulfilled the inclusion criteria. Any uncertainties were resolved by consensus or with a third reviewer (Jing Yang).

A predefined excel table was used to extract information about relevant characteristics of included studies such as title, the first author, publication year, sample size, age/gender of participants, follow-up times, TNM stage, treatment method, CRP level *et al.*

2.4. Quality Assessment

The quality of the methodology of the included studies was assessed by the Newcastle-Ottawa scale (NOS) recommended by the Cochrane Non-Randomized Studies Methods Working Group. Studies with scored ≥ 6 were defined as high quality studies. Quality assessment was performed by two investigators (Fu-Lun Li and Ke Liu) independently. Disagreements were resolved by discussion.

2.5. Statistical Analysis

The pooled *HR* and its 95% confidence interval (95%*CI*) was used to evaluate the correlation between CRP and poor

prognosis of gastric cancer patients; subgroup analysis was also performed by sample size, follow-up times, TNM stage and treatment method. Heterogeneity between studies was detected by the *Q* test and the *I*² metric (no heterogeneity: *I*²=0%-25%; moderate heterogeneity: 25%-50%; large heterogeneity: 50%-75%; and extreme heterogeneity: 75%-100%). A fixed effect model analysis was performed when *P* ≥ 0.10 in the *Q* test or when *I*² < 50%, otherwise a random effect model analysis was conducted. Publication bias were tested by the Begg's funnel plot. All *P* values were two-tailed and a *P* value less than 0.05 were considered statistically significant. Most of the statistical analyses in this study were conducted by the STATA software (version 11.2; Stata Corp, College Station, Texas USA).

3. Results

3.1. Search Results and Characteristics of Studies

Of 226 eligible papers identified in literature search, 18 papers [4, 6-22] fulfilled the inclusion criteria after screening the titles, abstracts and full texts, and removing the duplicates (shown in Figure 1). 16 of these studies were published in English and 2 in Chinese. Their sample size ranged from 53 to 466 subjects. The 18 included studies had a total 3656 subjects of which 2330 (63.70%) were males. Follow-up

times ranged from 1 month to 10 years. Moreover, all studies that scored ≥ 6 were considered to be of higher quality, which could be used for a meta-analysis (shown in Table 1).

3.2. CRP and the Poor Prognosis of Gastric Cancer Patients

18 studies evaluating the correlation between CRP lever and the poor prognosis of gastric cancer patients existed statistical heterogeneity ($I^2=85.2\%$, $P<0.001$). Therefore, the random effects model was used for meta-analysis. The results show that, CRP was significantly correlated with the poor prognosis of gastric cancer patients, high expression of C-reactive protein increases the risk of poor prognosis in patients with gastric cancer [HR (95% CI) =1.50 (1.24, 1.81)

$P=0.000$].

The different CRP level had different risks for the poor prognosis of gastric cancer patients, CRP cut-off points were 3mg/L, 5mg/L, 10mg/L, 17mg/L, 20mg/L and 120mg/L, and their HR (95% CI) were 1.92 (1.46, 2.52), 1.80 (0.68, 4.79), 1.46 (1.02, 2.08), 1.11 (1.04, 1.19), 2.03 (1.25, 3.30) and 1.77 (1.11, 2.82), respectively. When the optimal critical value of CRP lever were 10mg/L and 17mg/L, the risks of the poor prognosis of gastric cancer patients were lower. Unfortunately, there was only one literature which report the CRP cut-off points were 17mg/L. Therefore, when the $CRP>10mg/L$, the prognosis of gastric cancer patients was poor (the normal range for CRP is less than 10mg/L.) (shown in Figure 2).

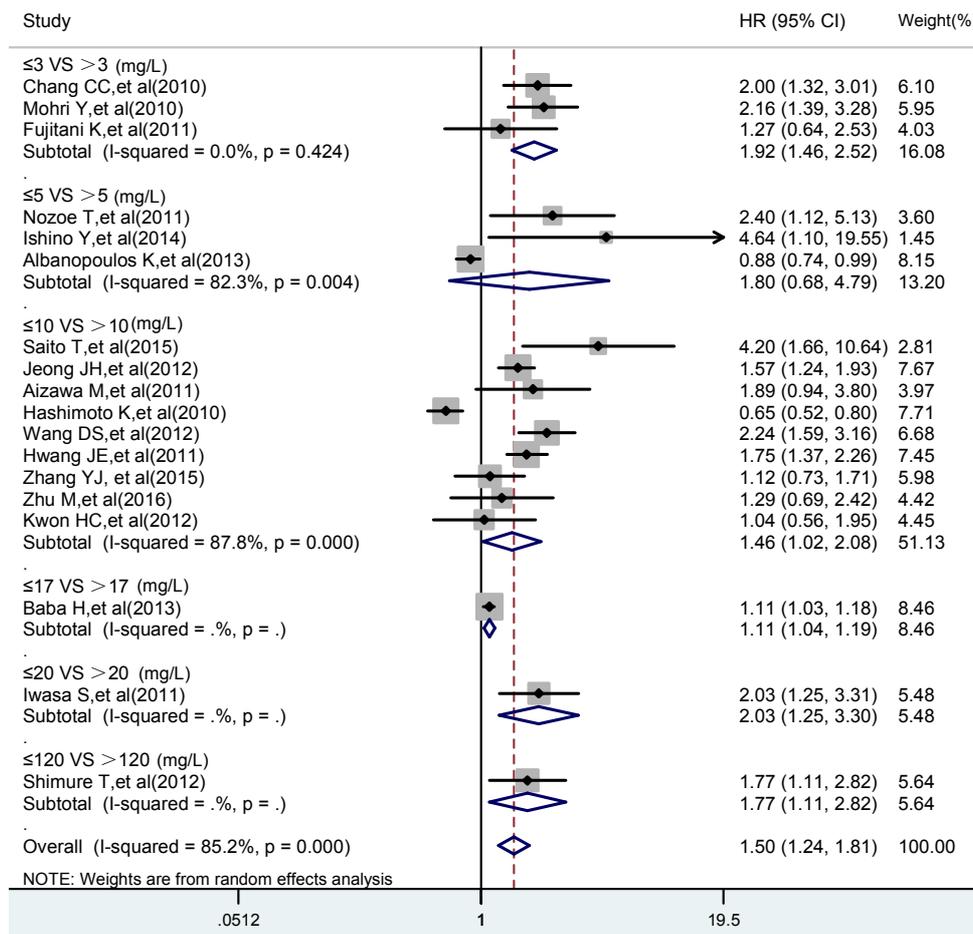


Figure 2. The risk of poor prognosis of gastric cancer patients in different CRP levels.

3.3. Subgroup Analyses of the Poor Prognosis of Gastric Cancer Patients

Subgroup analyses on sample size. As depicted in Table 2, the sample size was ≥ 200 , and there was statistical heterogeneity among the results of studies, so random effect model was used for analysis, HR (95% CI) was 1.78 (1.13, 2.81). Whereas, the sample size was <200 , the random effect model is also adopted, HR (95% CI) was 1.34 (1.10, 1.63). There is no statistical difference between the sample size ($P>0.05$). It suggested that the sample size included in the

study will not affect the risk of the poor prognosis of gastric cancer patients.

Subgroup analyses on follow-up times. As depicted in Table 2, the follow-up times (years ≥ 5 or <5) was significant heterogeneity. Using a random effects model, the follow-up times of year ≥ 5 and <5 HR (95% CI) was 1.61 (1.15, 2.26) and 1.49 (1.11, 2.00) respectively. There is no statistical difference between the follow-up times ($P>0.05$). It suggested the follow-up times will not affect the risk of the poor prognosis of gastric cancer patients.

Subgroup analyses on treatment method. As depicted in

Table 2, the significant differences were seen in the radical surgery group as calculated by the random effect model, *HR* (95%*CI*) was 1.40 (1.08, 1.80). Whereas, the non-operative treatment adopted the fixed effect model, *HR* (95%*CI*) was 1.68 (1.44, 1.97). There is no statistical difference between the treatment ($P>0.05$). It suggested the treatment method will not affect the risk of poor prognosis of gastric cancer patients.

Subgroup analyses on TNM stage. Using a random effects model, *HR* (95%*CI*) was 1.47 (1.15, 1.86) in the stage IV.

Whereas, the stage I-III adopted the fixed effect model, *HR* (95%*CI*) was 2.23 (1.76, 2.82). There is no statistical difference between the TNM stage ($P>0.05$). It suggested the TNM stage will not affect the risk of poor prognosis of gastric cancer patients (shown in Table 2). In addition, it is observed that the *HR* (95%*CI*) is 1.47 (1.15, 1.86) and 2.23 (1.76, 2.82) in the stage IV and I-III, so in the different stage, high expression of C-reactive protein can increase the risk of poor prognosis in patients with gastric cancer.

Table 2. Subgroup analyses for C-reactive protein and the risk of poor prognosis of gastric cancer patients.

Subgroup	Number of cohorts	<i>HR</i> (95% <i>CI</i>), <i>P</i>	<i>P</i> value	<i>I</i> ² %
Sample size	≥200	8	1.78 (1.13, 2.81), 0.013	0.879
	<200	10	1.34 (1.10, 1.63), 0.004	
Follow-ups (years)	≥5	6	1.61 (1.15, 2.26), 0.006	0.745
	<5	12	1.49 (1.11, 2.00), 0.008	
Treatment	Radical surgery	10	1.40 (1.08, 1.80), 0.010	0.883
	Non-surgery	3	1.68 (1.44, 1.97), 0.000	
TNM stage	IV	7	1.47 (1.15, 1.86), 0.002	0.991
	I-III	5	2.23 (1.76, 2.82), 0.000	

3.4. Multi-Factorial Analysis of the Poor Prognosis of Gastric Cancer Patients

Multiple factors affecting the risk of poor prognosis of gastric cancer patients included gender, age (years), lymphatic invasion, peritoneal metastasis and recurrence. As depicted in Table 3, it suggested that gender, age (years), lymphatic invasion were not the influencing factors of the

poor prognosis of gastric cancer patients ($P>0.05$), *HR* (95%*CI*) for gender, age (years) and lymphatic invasion were 1.04 (0.93, 1.17), 1.00 (0.87, 1.14) and 1.18 (0.64, 2.16) respectively. Whereas, *HR* (95%*CI*) for peritoneal metastasis and recurrence were 2.85 (1.26, 6.46) and 3.61 (2.46, 5.28). It showed peritoneal metastasis and recurrence are risk factors of the poor prognosis of gastric cancer patients ($P<0.05$) (shown in Figure 3).

Table 3. Multivariate analysis for the risk of poor prognosis of gastric cancer patients.

Factors	Analysis	Number of cohorts	<i>HR</i> (95% <i>CI</i>), <i>P</i>	<i>I</i> ² %
Gender	Male VS Female	11	1.04 (0.93, 1.17), 0.367	27.4
Age (years)	<60 VS ≥60	5	1.00 (0.87, 1.14), 0.949	0.0
Lymphatic invasion	Yes VS No	4	1.18 (0.64, 2.16), 0.990	59.6
Peritoneal metastasis	Yes VS No	3	2.85 (1.26, 6.46), 0.012	88.7
Recurrence	Yes VS No	2	3.61 (2.16, 5.28), 0.000	0.0

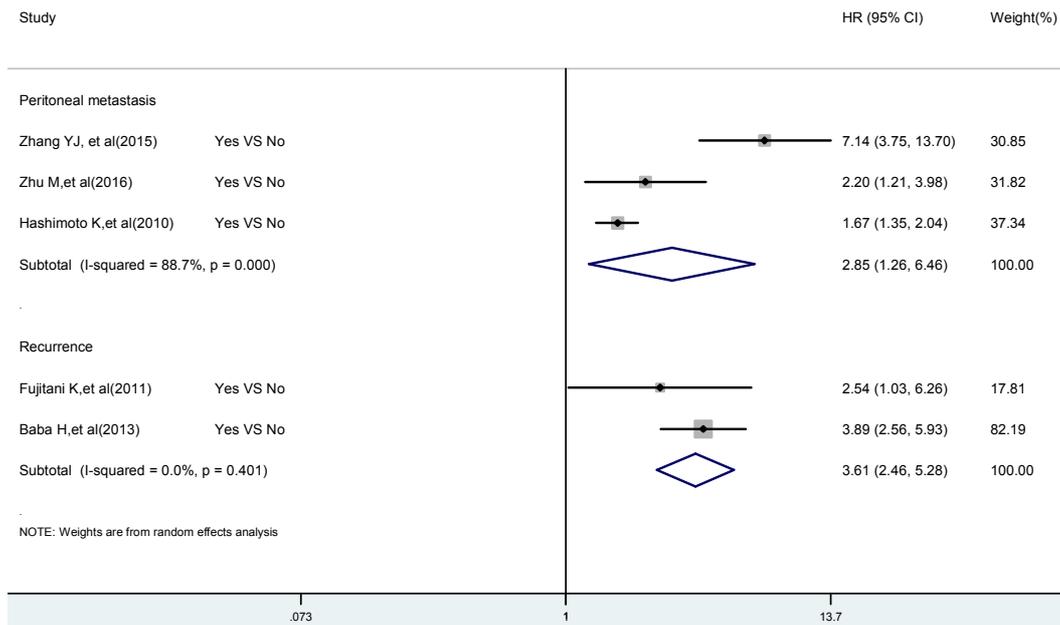


Figure 3. Peritoneal metastasis and recurrence for the risk of the poor prognosis of gastric cancer patients.

3.5. Sensitivity Analysis of the Meta-analysis

As depicted in Figure 4. Sensitivity analysis indicated that the results of the meta-analysis were stable.

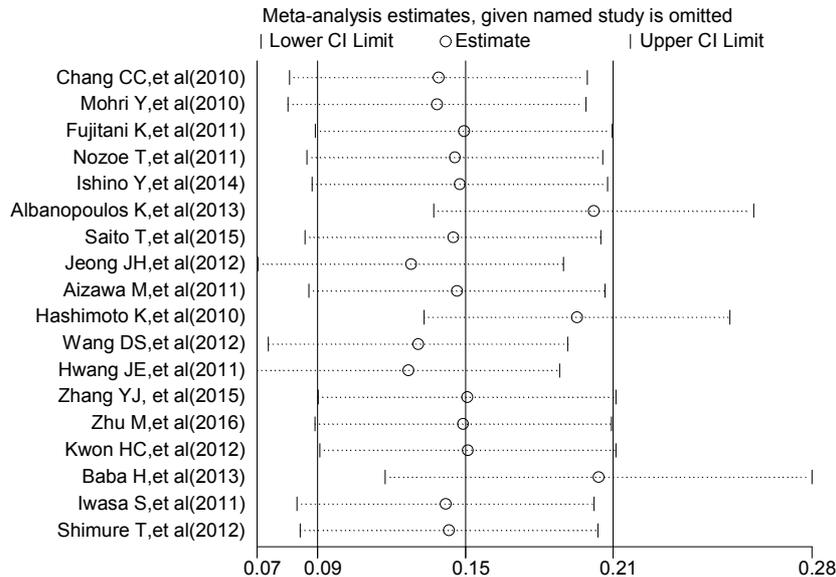


Figure 4. Sensitivity analysis for the risk of poor prognosis of gastric cancer patients at different CRP levels.

3.6. Publication Bias Analysis of the Meta-analysis

The potential reasons of Begg’s test to detect the publication bias. Each divergence point was basically symmetrically dispersed, and it was an inverted funnel shape ($P=0.131$), suggesting that the possibility of publication bias was less (shown in Figure 5).

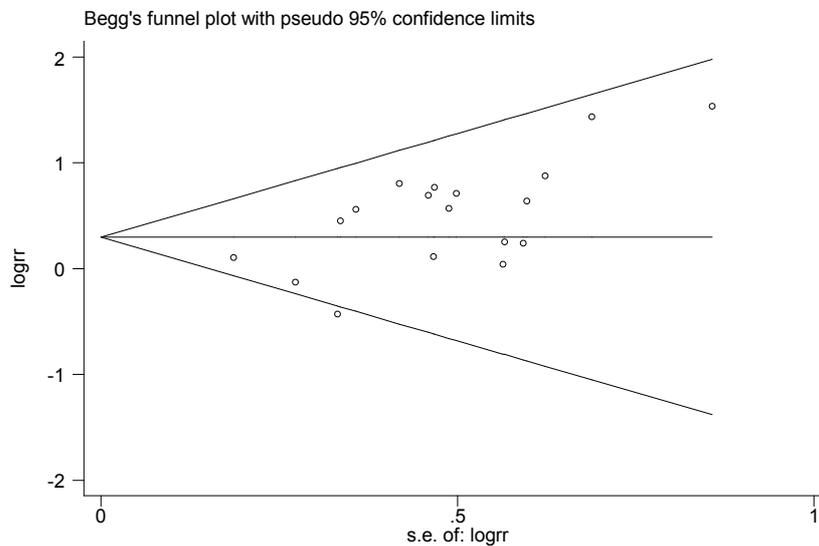


Figure 5. Begg’s funnel plots for the risk of poor prognosis of gastric cancer patients at different CRP levels.

4. Discussion

Cancer-associated inflammation is modulated by cancer cells themselves, host stromal cells, and their interactions. The CRP was an acute phase protein synthesized by hepatocytes, which reflected a measure of the acute phase response [23]. The molecular mechanism of the correlation between CRP and prognosis of cancer is complex and has not

yet been fully clarified. The mechanism was more widely recognized that cancer can raise CRP levels, and CRP promotes the occurrence and development of cancer. The mechanism of elevation of CRP caused by cancer was: Inflammatory mediators and cytokines were produced or released by endogenous and exogenous stimuli, such as cancer. Activated inflammatory cells released TNF and IL-1, which acted on lymphocytes and stromal cells to release IL-

6, IL-8 and macrophage inflammatory proteins. These cytokines acted on blood vessels, including the liver, to produce acute phase reaction proteins such as CRP [24, 25]. The mechanism of promoting cancer development by CRP was: Chronic inflammation and oxidative stress inactivated cancer suppressor genes or inhibited protein post-translational modifications (PTMs) regulating DNA repair and apoptosis; inflammatory cytokine signals promoted the proliferation of cancer cells and inhibited apoptosis of cancer cells via intracellular enzymes and transcription factors. Moreover, activation of inflammatory pathways can promote cell migration, vascular infiltration and angiogenesis, further accelerate cancer progression [26, 27].

An effective prognostic indicator could not only predict the survival condition, but also provide guidance for doctors in the selection of clinical treatment, correct selection of clinical treatment method would improve the quality of life in patients. At present, there are many researches on the correlation between CRP level and gastric cancer, but whether CRP could be used as an evaluation indicator for prognosis of gastric cancer patients, which was still controversial. Therefore, we deeply analyzed the published cohort study on CRP level and the risk of poor prognosis of gastric cancer patients, in order to determine the dose-relationship between CRP and the risk of poor prognosis of gastric cancer patients.

There had been a lot of researches on the correlation between CRP and the occurrence or prognosis of gastric cancer at home and abroad. Baba *et al.* [8] found CRP was a risk factor for poor prognosis of gastric cancers in stage IV [HR (95% CI) 1.11 (1.03, 1.18)], which was consistent with our study results [HR (95% CI)=1.50, (1.24, 1.81)]. Baba *et al.* [8] found the optimal critical value of CRP was 17mg/L by ROC curve. That is to say when $CRP > 17mg/L$, the risk of the poor prognosis of gastric cancer patients was significantly increased. Meanwhile our study also found that when the critical value of CRP was 10mg/L and 17mg/L, the risk of poor prognosis was lower than others. A recent Meta study [28] found that when $CRP > 10mg/L$, accompany with the increase of CRP the risk of the poor prognosis of gastric cancer patients was significantly increased, which was consistent with our study results. Subgroup analysis showed that in the different stage, high expression of C-reactive protein can increase the risk of poor prognosis of gastric cancer patients. Multivariate analysis showed that peritoneal metastasis and recurrence could increase the risk of poor prognosis of gastric cancer patients, which is consistent with that obtained by Yu [28].

5. Conclusions

In conclusion, this study showed that: 1) the CRP level was closely related to the risk of poor prognosis of gastric cancer patients; 2) when $CRP > 10mg/L$, CRP can be used as an important indicator of poor prognosis of gastric cancer patients; 3) in the different clinical stage high expression of C-reactive protein both can increase the risk of poor

prognosis of gastric cancer patients; 4) multivariate analysis showed that peritoneal metastasis and recurrence were the factor independently associated with prognosis of gastric cancer patients.

In the future, more high-quality, multi-center and large-scale clinical trials need to be carried out to further prove this result. It is believed that breakthrough progress will be made in evaluating the prognosis of gastric cancer patients, and early intervention treatment will improve the quality of life of cancer patients.

Conflicts of Interest

- 1) All the authors do not have any possible conflicts of interest.
- 2) The authors declare that they have no competing interests.

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