RESEARCH ARTICLE

Prognostic Value of C-Reactive Protein in Esophageal Cancer: a Meta-analysis

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Abstract

Background: The classical inflammatory biomarker, C-reactive protein (CRP), has been identified to be related to progression of esophageal cancer. Some research showed that elevated pretreatment serum CRP indicated a poor prognosis, but results have been inconsistent. Materials and Methods: We searched the Medline, Embase and the Cochrane Central Search Library for suitable studies and a meta–analysis of eleven (1,886 patients) was conducted to examine the relationship between elevated serum CRP level and overall survival (OS) in esophageal cancer cases. Moreover, correlation analyses were conducted to assess links between pretreatment serum CRP level and tumor node metastasis (TNM) stage as well as T, N, M grade, respectively. Results: The pooled analysis showed that elevated pretreatment serum CRP level was significantly associated with poorer overall survival (HR 2.09, 95% CI 1.52-2.87, $p<0.01$). Subgroup analyses were conducted by "country", "cut-off value", "treatment" and "number of patients", and no single factor could alter the result. Elevated pretreatment serum CRP was significantly correlated with more advanced TNM stage and T, N, M grade respectively. Conclusions: Elevated pretreatment serum CRP levels are associated with poorer prognosis in esophageal cancer patients, and could serve as a useful biomarker for outcome prediction.

Keywords: C-reactive protein - esophageal cancer - prognosis - meta-analysis

Asian Pac J Cancer Prev, **15 (19)**, 8075-8081

Introduction

Esophageal cancer is the sixth cause of cancer deaths in the world, and the fourth cause of cancer deaths in China (Jemal et al., 2011). Multidisciplinary treatment strategies based on surgery, chemotherapy and radiotherapy have provided significant improvement in outcome of esophageal cancer patients. Unfortunately, due to the relatively late stage of diagnosis and rapid progress of tumor, the prognosis is disappointing (Vallbohmer et al., 2006). The tumor-node-metastasis (TNM) staging system and tumor markers, such as carcinoembryonic antigen (CEA) and CYFRA21-1, have made great contributions to the selection of treatment strategies. However, the great differences in survival within the same pathological TNM stage indicate that present system can not satisfy the clinical requirement. Therefore, it is important for clinicians to find a simple and effective biomarker to provide advice on the selection of clinical strategies.

C-reactive protein (CRP), which named for its capacity to precipitate the C-polysaccharide of *Streptococcus pneumonia*, is a classical acute phase protein that participates in the host defense (Janeway et al., 2002). The serum CRP elevates significantly during acute inflammation, so it is common to use serum CRP as a sensitive marker of inflammation in clinical. However, CRP is also a nonspecific biomarker, and the elevation of CRP is observed under the conditions of myocardial infarction, trauma and cancer (Gabay et al., 1999). Recently, the relationship between CRP and prognosis of cancer was further investigated in renal cell carcinoma (Hu et al., 2014), gastric cancer (Yu et al., 2013), hepatocellular carcinoma (Zheng et al., 2013) and lung cancer (Zhou et al., 2012).

However, there has not been definitive conclusion on the relation between serum CRP level and prognosis of esophageal cancer. Some researches showed that the overall survival (OS) was significantly shorter in the esophageal cancer patients with elevated serum CRP level (Feng et al., 2013; Song et al., 2013). However, some researches showed that the correlation between elevated serum CRP level and shorter OS was not statistically significant (Miyata et al., 2011). Due to the small sample size of the individual studies, the current opinion is still controversial. In this study, we conducted a meta-analysis to assess the correlation of elevated serum CRP level with

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the OS of esophageal cancer patients. In addition, the relationship between elevated CRP and TNM stage was also investigated.

Materials and Methods

Search strategy

We searched the Medline, Embase and the Cochrane Central Search Library for published studies that referred to the prognostic value of CRP in primary esophageal cancer up to April 30, 2014. The following search terms were used as MeSH terms and keywords: "esophageal cancer", "C-reactive protein", "CRP" or "prognosis".

Study inclusion/ exclusion criteria

Studies were considered eligible for meta-analysis if they met all the following criteria: (1) Patients were pathologically diagnosed as primary esophageal cancer; (2) The serum CRP level was measured before treatment, and the cut-off value of CRP was reported; (3) The relationship between the OS of patients and the serum CRP level was reported, or the relationship between TNM stage and the serum CRP level was reported; (4) The language was limited to English. Studies were excluded if they met one of the following criteria: (1) Repeated reports or duplicate data; (2) Case report, review, letter, animal model or cell line research; (3) Literature with the sample size less than 30; (4) No sufficient data to extract the hazard ratio (HR) or odds ratio (OR).

Table 1. Newcastle-Ottawa Quality Assessment Scale

Selection
- 1) Representativeness of the exposed cohort
  - a) Truly representative of the average esophageal cancer patients in the community*
  - b) Somewhat representative of the average esophageal cancer patients in the community*
  - c) 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
- 1) Comparability of cohorts on the basis of the design or analysis
  - a) Study controls for metastasis or recurrence*
  - b) Study controls for 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%) 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

Study quality assessment

The quality assessment was performed by three independent reviewers (Cao, Li and Liang) according to the Newcastle-Ottawa Quality Assessment Scale (Table 1) (Stang, 2010). This scale is an eight-item instrument that allows for quality assessment of studies for meta-analysis. The assessment is performed by awarding "stars" for high quality studies. Stars are added up and used to quantitatively compare the quality of studies.

Data extract

Two independent reviewers (Cao and Li) reviewed the included studies and extracted data independently. If the two reviewers had disagreements, a third reviewer (Guo) reviewed the studies and extracted data independently. The three groups of data were compared together, and the best one was selected. The extracted data elements included "author", "year", "country", "sample size", "mean or median age", "median follow-up periods", "treatment method", "TNM stage", "T, N, M grade", "cut-off value", HRs for the correlation between CRP and OS, and ORs for the correlation between CRP and TNM-related information.

Data analysis

The pooled HR and 95%CI were selected to estimate the relationship between CRP level and OS. The HRs and 95%CIs of included studies were obtained directly from published data. Subgroup analyses were designed by stratifying the included studies by "country", "cut-off value", "treatment", "number of patients". The pooled

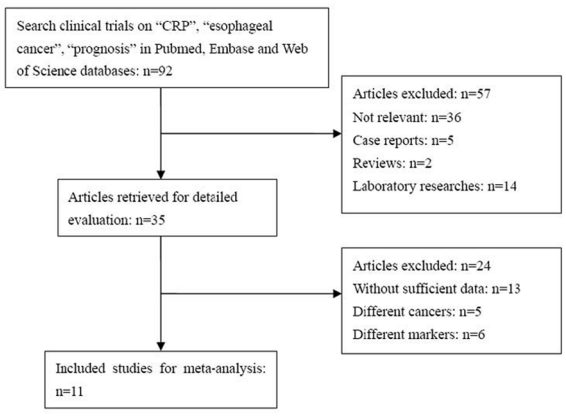

Figure 1. Flow Chart of the Meta-Analysis

ORs and 95%CIs were selected to estimate the relationship between CRP level and TNM stage, T grade, N grade and M grade respectively. The heterogeneity of pooled HRs and ORs were evaluated by inconsistency index I^2. P<0.1 or I^2>50% indicated a significant heterogeneity (Higgins et al., 2003). Pooled HR>1 indicated a worse outcome of OS for higher CRP, and the difference was statistically significant if p<0.05. Assessment of publication bias was evaluated by the Begg's funnel plot and Egger's bias indicator test (Egger et al., 1997). All statistical analyses were performed using the statistical software Stata version 12.0.

Results

Search results

According to the search strategies as described, 92 studies were identified. After reviewing the titles and abstracts, 57 studies were eliminated, and the remaining 35 studies were retrieved for detailed information. After further investigating the studies, 24 studies were screened out due to insufficient data or different cancers. Finally, 11 studies were eligible for meta-analysis (Nozoe et al., 2001; Ikeda et al., 2003; Shimada et al., 2003; Guillem et al., 2005; Gockel et al., 2006; Wang et al., 2009; Fujiwara et al., 2011; Miyata et al., 2011; Feng et al., 2013; Meng et al., 2013; Song et al., 2013). The flow chart of search process was shown in Figure 1.

The characteristics of 11 studies were listed in Table 2. Among these studies, 5 studies were performed in Japan, 4 in China, 1 in France and 1 in Germany. The 11 studies included a total of 1886 patients, with a median sample size of 152 patients, ranging from 34 to 356. There were 1598 male and 288 female patients respectively, with the mean/median ages ranging from 54.0 to 66.5 years. There were 4 studies with the operation treatment alone, and the other 7 studies treated patients with multiple therapies, which indicated multiple strategies among neoadjuvant therapy, chemotherapy, radiotherapy and operation. The cut-off values of CRP varied from 2mg/l to 10mg/l, and most studies set 5mg/l or 10mg/l as cut-off values. HRs were recorded in 8 studies, and all the studies recorded TNM-related information. The study quality points ranged from 6 to 8.

Serum CRP level and OS in esophageal cancer

Eight studies reported the relationship between serum CRP level and OS in esophageal cancer patients (Nozoe et al., 2001; Ikeda et al., 2003; Shimada et al., 2003; Wang et al., 2009; Miyata et al., 2011; Feng et al., 2013; Meng et al., 2013; Song et al., 2013). The heterogeneity

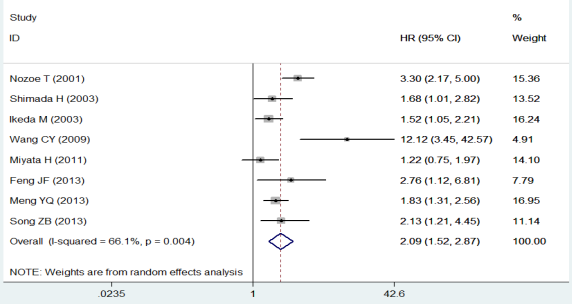

Figure 2. Forest Plot of Association Between Elevated CRP Level and Poor OS in Esophageal Cancer

Table 2. Characteristics of Included Studies

Study	Year	Country	Sample size (n, M/F)	Mean/median age(years)	Median follow-up periods (months)	Treatment
Nozoe T et al.	2001	Japan	262(227/35)	NR	NR	Multiple therapies
Shimada H et al.	2003	Japan	150(128/22)	65(35-87)	NR	Operation
Ikeda M et al.	2003	Japan	356(327/29)	65(22-87)	33.6(1-145)	Multiple therapies
Guillem P et al.	2005	France	67(62/5)	62.6(46-83)	NR	Multiple therapies
Gockel I et al.	2006	Germany	291(240/51)	59(28-79)	NR	Operation
Wang CY et al.	2009	China	123(120/3)	54(34-81)	23(3-57)	Multiple therapies
Miyata H et al.	2011	Japan	152(132/20)	62.5(54.1-70.9)	60.2(20.1-120.8)	Multiple therapies
Fujiwara et al.	2011	Japan	34(6/28)	66.5(52-78)	NR	Multiple therapies
Feng JF et al.	2013	China	43(30/13)	58.7(50.9-66.5)	NR	Multiple therapies
Meng YQ et al.	2013	China	252(192/60)	57.33(31-82)	65.5(1-78)	Operation
Song ZB et al.	2013	China	156(134/22)	59(31-78)	56(12-84)	Operation

Study	Cut-off value	No. patient with high CRP	T grade	N grade	M grade	TNM stage	Study quality points
Nozoe T et al.	≥5mg/l	84	Tis-T4	N0, N1	NR	0-IV	6
Shimada H et al.	≥10mg/l	35	T1-T4	N0, N1	M0, M1	I-IV	7
Ikeda M et al.	≥5mg/l	149	NR	NR	NR	I-IV	7
Guillem P et al.	≥6mg/l	35	T1-T4	N0, N1	M0, M1	NR	6
Gockel I et al.	≥5mg/l	164	T1-T4	N0, N1	M0, M1	NR	7
Wang CY et al.	≥5mg/l	81	T1-T4	N0, N1	M0, M1	NR	8
Miyata H et al.	≥10mg/l	43	T1-T4	N0, N1	NR	II-IV	7
Fijiwara et al.	≥3mg/l	23	T3, T4	N0, N1	M0, M1	II-IV	7
Feng JF et al.	≥10mg/l	16	T1-T4	N0, N1	NR	NR	8
Meng YQ et al.	≥2mg/l	98	T1-T4	N0, N1	NR	I-IV	6
Song ZB et al.	≥5mg/l	39	T1, T2	N0	M0	I, II	6

*M/F, male/female; Multiple therapies include at least two kinds of therapy strategies among radiotherapy, chemotherapy and operation; Operation means that patients only receive operation therapy; NR, not record; Study quality points are calculated using the Newcastle-Ottawa quality assessment scale

Table 3. Subgroup Analyses of Pooled HR for High Serum CRP Expression and OS in Esophageal Cancer

Subgroup		No. of cohorts	No. of patients	Pooled HR (95% CI)	P value	Heterogeneity	
						I^2 (%)	P value
Country	China	4	574	2.74 (1.51, 4.94)	0.001	64.50%	0.037
	Japan	4	920	1.80 (1.17, 2.78)	0.007	73.80%	0.01
Cut-off value	≥10mg/l	3	345	1.58 (1.08, 2.33)	0.02	23.30%	0.271
	≥5mg/l	4	897	2.81 (1.51, 5.22)	0.001	79.20%	0.002
Treatment	Surgery	3	558	1.83 (1.42, 2.37)	0	0.00%	0.854
	Multiple therapies	5	936	2.45 (1.39, 4.34)	0.002	80.00%	0
Number of patients	≥200	3	870	2.07 (1.35, 3.18)	0.001	74.60%	0.019
	≤200	5	624	2.24 (1.30, 3.86)	0.004	68.00%	0.014

*HR, Hazard ratio; CI, confidence interval

Table 4. Correlation Analyses on Increased CRP and T grade, N grade, M grade and TNM Stage in Esophageal Cancer

Classification	No. of cohorts	No. of patients	OR (95% CI)	P value	Heterogeneity	
					I^2 (%)	P value
TNM stage(III/IV *vs* I/II)	4	698	2.82 (2.01, 3.95)	0	53.90%	0.089
T grade (T3-4 *vs* T1-2)	6	1034	2.44 (1.83, 3.25)	0	45.60%	0.102
N grade (N1 *vs* N0)	8	1217	1.81 (1.41, 2.33)	0	23.80%	0.24
M grade(M1 *vs* M0)	5	657	1.95 (1.29, 2.94)	0.002	51.00%	0.086

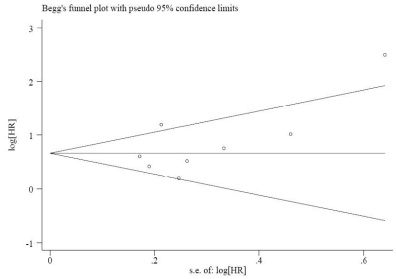

Figure 3. Begg's Funnel Plot for the Publication Bias of the Included Studies

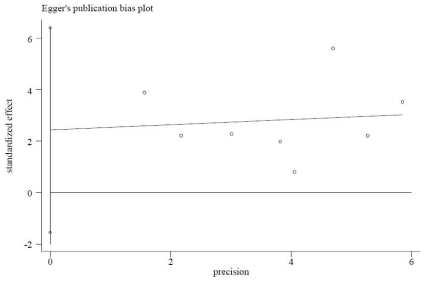

Figure 4. Egger's Plot for Publication Bias of the Included Studies

test indicated there was significant heterogeneity among included studies (I^2=66.1%, p=0.004), thus a random effects model was employed to obtain the pooled HR. The statistical result showed that the elevated serum CRP level was significantly correlated with poor OS (HR 2.09, 95%CI 1.52-2.87, p<0.01) (Figure 2).

In order to further investigate the relationship between elevated CRP level and poor OS, subgroup analyses were generated. The 8 studies were re-grouped by "country", "cut-off value", "treatment" and "number of patients".

When stratified by "country", the "China" group included 4 studies, and the HR was 2.74, with 95%CI 1.51-4.94. The "Japan" group included 4 studies, and the HR was 1.80, with 95%CI 1.17-2.78.

When stratified by "cut-off value", the "≥10mg/l" group included 3 studies, and the HR was 1.58, with 95%CI 1.08-2.33. The "≥5mg/l" group included 4 studies, and the HR was 2.81, with 95%CI 1.51-5.22. We should notice that only 7 studies were included in the subgroup analysis, and one study (Meng et al., 2013) was excluded from subgroup analysis because it selected "≥2mg/l" as cut-off value, which was generated from the receiver operating characteristic (ROC) curve.

When stratified by "treatment", the "surgery" group included 3 studies, and the HR was 1.83, with 95%CI 1.42-2.37. The "multiple therapies" group included 5 studies, and the HR was 2.45, with 95%CI 1.39-4.34.

When stratified by "number of patients", the "≥200" group included 3 studies, and the HR was 2.07, with 95%CI 1.35-3.18. The "≤200" group included 5 studies, and the HR was 2.24, with 95%CI 1.30-3.86.

The detailed results of subgroup analyses were shown in Table 3.

Serum CRP level and TNM-related information in esophageal cancer

There were 4 studies (Nozoe et al., 2001; Shimada et al., 2003; Fujiwara et al., 2011; Meng et al., 2013) reported the data regarding the relationship between serum CRP and TNM stage (III/IV *vs* I/II) of esophageal cancer. Elevated serum CRP value was significantly correlated with advanced TNM stage, and the OR was 2.82, with 95%CI 2.01-3.95.

The T, N, M grade played an important rule in the prognosis of esophageal cancer, thus we performed correlation analyses between serum CRP level and T, N, M grade respectively. Six studies referred to the relationship between elevated serum CRP level and T grade (T3-4 *vs* T1-2), and the OR was 2.44, with 95%CI 1.83-3.25. Eight studies referred to the relationship between elevated serum CRP level and N grade (N1 *vs* N0), and the OR was 1.81, with 95%CI 1.41-2.33. Five studies referred to

the relationship between elevated serum CRP level and M grade (M1 *vs* M0), and the OR was 1.95, with 95%CI 1.29-2.94. The results showed that elevated serum CRP level was correlated with higher stages of T, N and M grade. The detailed information was shown in Table 4.

Publication bias

Begg's and Egger's test were adopted to assess the publication bias of 8 included studies for OS. The P values indicated that there was no significant publication bias in OS (Begg's test: p=0.138, Egger's test: p=0.186) (Figure 3 and Figure 4).

Discussion

The TNM staging system has made great contributions to the evaluation of prognosis and decision-making of treatment in esophageal cancer. This system is designed based on the biological behavior of cancer cells, such as tumor location, lymph node metastasis and distant metastasis. However, the current viewpoint considers cancer as a systemic disease, and many factors can affect the progression and prognosis of cancer, including socioeconomic status, immune status and inflammation. Conversely, the progression of cancer can also cause influence on these factors (Vakkila et al., 2004; Zeh et al., 2005; Holmes et al., 2007). It is common that even if patients are in the same TNM stage and receive the same therapy strategy, the outcomes can vary greatly. This phenomenon suggests that prognostic value of TNM staging system alone is far from satisfactory. We need to establish a comprehensive system for the evaluation of patient status and selection of optimal therapy strategies.

CRP has been used as a sensitive but non-specific inflammation biomarker for more than 80 years. Recently more and more researches have focused on the prognostic value of CRP in cancers. It is shown that elevated CRP level predicts a worse outcome in cancer patients, especially in gastric cancer and urological cancer (Guo et al., 2013; Yu et al., 2013; Dai et al., 2014). However, the relationship between elevated CRP level and the prognosis of esophageal cancer is unclear, and there is a lack of large scale, multicentric clinical trial to solve this problem. In this meta-analysis, we first investigated the relationship between CRP and OS in esophageal cancer. Our results showed that high serum CRP was significantly associated with poor OS (HR 2.09, 95%CI 1.52-2.87, p<0.05). A significant heterogeneity was observed (I2=66.1%, p=0.004), and the heterogeneity consistently existed when deleting each study. Thus we selected a random effect model to analyze the pooled HR, and conducted subgroup analyses to evaluate the source of heterogeneity.

The morbidities of esophageal cancer vary greatly in different regions. In the high incidence area, such as East and West Asia, the morbidity can be 16-fold higher than low incidence area West Africa and Central America. In China, the morbidity in northern region can be much higher than other regions (Jemal et al., 2011). So the regional difference of included studies has great impact on the final result. Besides, the CRP test method and cut-off value also affect the homogeneity of the results. Compared with other treatment strategies, radical operation is the only treatment that can cure esophageal cancer, thus whether the treatment strategies contain operation has great influence on the prognosis. The sample size can also affect the stability of conclusion. In order to evaluate the source of heterogeneity, we divided the studies by "country", "cut-off value", "treatment" and "number of patients". All the results in individual subgroup indicated that high serum CRP was significantly associated with poor OS. Significant heterogeneity existed in most subgroups, and just in "cut-off value≥10mg/l" subgroup and "surgery" subgroup the heterogeneity was not observed. TNM staging system is the classic method in tumor evaluation and prognosis prediction, so we explored the correlation between increased CRP and TNM stage. The results showed that elevated CRP level predicted advanced TNM stage and T, N, M grade respectively. This implies that CRP is not an independent prognosis factor for esophageal cancer. This conclusion is correlated with other researches (Guo et al., 2013; Yu et al., 2013; Hu et al., 2014). A new predictive model that includes CRP and TNM stage has been developed to evaluate the prognosis of clear cell renal cell carcinoma (Iimura et al., 2009).

The molecular mechanism of CRP in the progression of esophageal cancer remains unclear. Persistent inflammatory status plays an important role in the development of cancers (Vakkila et al., 2004). Viral infections such as human papilloma virus (HPV), herpes simplex virus (HSV) and Epstein-Barr virus (EBV) are thought to be risk factors of esophageal cancer (Lyronis et al., 2005). Besides, gastroesophageal reflux disease is associated with adenocarcinoma of esophagus (Mayne et al., 2002). All these risk factors can cause esophageal cancer by inducing chronic inflammation. Various cytokines secreted by inflammatory cells, particularly IL-6, can stimulate the growth of esophageal cancer cells, and promote hepatocytes to produce acute phase protein such as CRP. On the other hand, the tumor tissue itself can trigger inflammatory response. The rapid growth of tumor tissue causes regional necrosis, which further induces the accumulation of inflammatory cells and the release of proinflammatory cytokines such as TGF-β, TNF-α, IL-6 and IL-11 (Vakkila et al., 2004). After being released into blood, these cytokines can stimulate hepatocytes to synthesize acute phase protein, including CRP. Traditionally, CRP is mainly synthesized by hepatocytes. However, recent researches found that esophageal cancer tissue also had the ability to synthesize CRP alone. The expression of CRP in esophageal cancer tissue was significantly higher than normal tissue, and CRP expression was an independent prognostic factor of survival in esophageal cancer patients (Nozoe et al., 2003; Nakatsu et al., 2012). Moreover, the genetic polymorphism of CRP is associated with lymph node metastasis. The CRP 1846C>T polymorphism predicted lymph node metastasis more accurately than computed tomography (Motoyama et al., 2013). Single nucleotide polymorphisms of CRP are also related to risk and prognosis of cancer patients, and genotype CC of rs1800947 in CRP has been shown to be associated with increased cancer risk (Chen et al., 2014). These findings suggest that CRP not only exists

as a marker of inflammation, but also has some unknown effects on the proliferation and metastasis of esophageal cancer. However, further researches are required to investigate these effects.

Notably, some limitations should not be ignored in this meta-analysis. First, the literatures were only from limited databases, and the unpublished literatures were excluded. The number of included studies and total sample size were limited. Second, most included studies were retrospective because of the lack of prospective studies. Moreover, because the morbidities, pathological types and treatment of esophageal cancer varied greatly in different regions, the heterogeneity was significant. However, based on the random effects model, the final results were reliable. The heterogeneity could be reduced by organizing large scale and multicenter studies that had unified diagnosis and treatment criteria.

In conclusion, our meta-analysis demonstrated that elevated pretreatment serum CRP level was significantly correlated with a worse OS and more advanced TNM stage. As a cheap and simple biomarker, CRP is a valuable prognostic factor for esophageal cancer. The combination of pretreatment serum CRP level and TNM stage is a promising strategy for the prediction of prognosis and selection of treatment.

Acknowledgements

This study was supported by the Youth Innovation Fund Project of the First Affiliated Hospital of Zhengzhou University. The authors declared that they had no competing interests.

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