

Prognostic role of serum C-reactive protein in esophageal cancer: a systematic review and meta-analysis

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Background: Recent studies have shown that C-reactive protein (CRP) is a useful predictive factor in several cancers; however, its role in esophageal cancer (EC) is controversial.

Methods: A systematic literature search was performed using Medline, PubMed, and Web of Science to analyze the prognostic value of serum CRP in patients with EC. A meta-analysis was performed to assess the association between serum CRP and overall survival (OS) in patients with EC.

Results: A total of eight studies involving 1,471 patients were included in our study. Our pooled results demonstrated that a high level of serum CRP was associated with poor OS (hazard ratio [HR]: 1.40, 95% confidence interval [CI]: 1.25–1.57, $I^2=81.3\%$, $P<0.0001$). Subgroup analyses were performed in further investigations. When the patients were segregated according to treatment, pathological type, and cut-off level, high levels of serum CRP were found to be significantly correlated with OS.

Conclusion: Our meta-analysis revealed that high levels of serum CRP were significantly associated with poor OS in patients with EC.

Keywords: CRP, esophageal cancer, meta-analysis

Introduction

Esophageal cancer (EC) is the eighth most frequent cancer and the sixth leading cause of cancer death worldwide.¹ Surgical resection remains the modality of choice, however, the prognosis is poor.² The reason for this may be the relatively late stage of diagnosis and rapid progression.^{3,4} Thus, it is important for us to identify predictive factors for the prognosis in patients with EC.

In an attempt to better estimate the prognosis, many prognostic factors have been investigated, such as depth of invasion, nodal metastasis, tumor-node-metastasis (TNM) stage, and other miscellaneous factors.^{5,6} Recently, systemic inflammatory response (SIR) has been found to play an important role in cancer.^{7,8} Serum C-reactive protein (CRP) is a very sensitive indicator of SIR, and was initially identified in the plasma of patients as a substance reacting with pneumococcal C-polysaccharide, which appeared in patients with inflammation.^{9–11} CRP is synthesized mainly by hepatocytes as a part of the SIR.^{12,13} CRP is a representative acute-phase reactant and is the most widely used systemic biomarker of inflammation.^{14,15}

Previously published studies have shown that serum CRP is a predictor of survival in several cancers, such as gastric cancer,^{16,17} colorectal cancer,^{18,19} pancreatic cancer,²⁰ hepatocellular cancer,²¹ urological cancer,²² ovarian cancer,²³ lymphoma,²⁴

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and osteosarcoma.²⁵ Similar results have also been found in patients with EC.^{26–33} Nozoe et al²⁶ and Ikeda et al²⁷ demonstrated that CRP can be an independent marker in patients with EC. Gockel et al²⁹ investigated 291 EC patients who underwent curative resection, and they concluded that a high level of CRP is associated with tumor progression and poor overall survival (OS). This observation is in line with data from Wang et al,³⁰ Feng et al³² and Song et al³³ but is contrary to the results of Shimada et al²⁸ and Zingg et al³¹ who suggested that CRP is not an independent factor. Due to the inconsistent results, the role of serum CRP in EC is still controversial. In this study, therefore, we conduct a systematic review and meta-analysis to analyze the prognostic value of serum CRP for OS in patients with EC.

Materials and methods

Literature search

A systematic literature search was performed using Medline, PubMed, and Web of Science to analyze the prognostic value of CRP in patients with EC from 1984 to 2013. The search strategies included the keywords “C-reactive protein” or “CRP” combined with “esophageal cancer” or “esophageal carcinoma”. All selected studies were English language articles. Only human research was included. In addition, the reference lists of the identified studies were checked for further relevant studies.

Inclusion/exclusion criteria

Inclusion criteria for this meta-analysis were as follows: 1) patients were diagnosed as having EC by pathology; 2) the serum CRP was measured before treatment; 3) the relationship between CRP and OS was reported. The exclusion criteria were: 1) review, letter, case report, or nonhuman research; 2) insufficient data to extract the hazard ratio (HR) and the 95% confidence interval (CI).

Data extraction

Three authors (Huang, Feng, and Liu) reviewed the included studies and extracted the data independently. If the results reported overlapped, only the most recent or the most complete study was used in the meta-analysis. The extracted data included “authors”, “year”, “sample”, “country”, “treatment”, “pathological type”, “cut-off level”, “TNM stage”, and HR and 95% CI for the correlation between serum CRP and OS.

Statistical analysis

All statistical analyses were performed using Stata version 12.0 (StataCorp LP, College Station, TX, USA). The

pooled HR and 95% CI were used to analyze the relationship between CRP and OS. A significant heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$.³⁴ A combined HR > 1 indicated a worse OS, and it was considered statistically significant if the 95% CI did not overlap.

Results

According to the search strategies described, a total of 82 studies were identified. The search results are shown in Figure 1. After reviewing all 82 studies carefully, eight eligible studies, including 1,471 patients with EC, were included in the meta-analysis.^{26–33} The main characteristics of the eight included studies are listed in Table 1. Among these studies, three were performed in Japan,^{26–28} two in the People's Republic of China,^{32,33} one in Germany,²⁹ one in Taiwan,³⁰ and one in Australia.³¹ Five studies set a cut-off value of 5 mg/L,^{26,27,29,30,33} and three studies set a cut-off value of 10 mg/L.^{28,31,32}

Our pooled results demonstrated that high levels of serum CRP were associated with poor OS in patients with EC (HR: 1.40, 95% CI: 1.25–1.57). The analysis showed a significant heterogeneity for OS ($I^2 = 81.3\%$, $P < 0.0001$) (Figure 2). In further investigations, subgroup analyses were also performed in our meta-analysis. When the patients were segregated according to treatment, pathological type, and cut-off level, high levels of serum CRP were also found to be significantly correlated with OS (Table 2; Figure 3A–F).

Discussion

In this meta-analysis, our pooled results demonstrated that high levels of serum CRP were associated with poor OS in patients with EC (HR: 1.40, 95% CI: 1.25–1.57). There was a significant heterogeneity for OS ($I^2 = 81.3\%$, $P < 0.0001$). We did further subgroup analyses to evaluate the correlation between serum CRP and OS in the included studies.

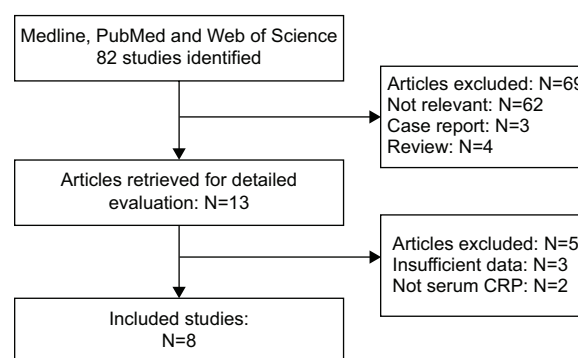


Figure 1 Flow chart of the meta-analysis.
Abbreviation: CRP, C-reactive protein.

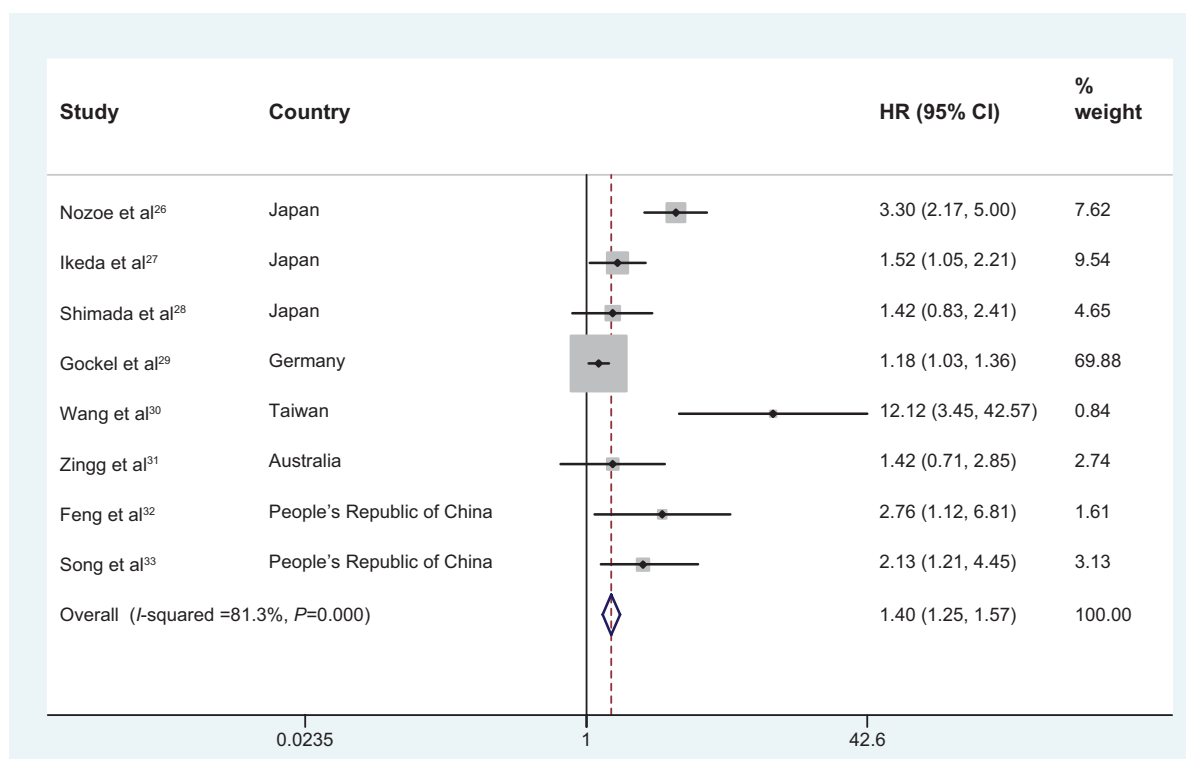
Table 1 Characteristics of included studies

Author	Year	Country	Sample (M/F)	Treatment	Survival analysis	Pathological type	HR (95% CI)	Cut-off level (mg/L)	TNM stage I–II/III–IV
Nozoe et al ²⁶	2001	Japan	262 (227/35)	C/R + S	OS	SCC + AC	3.300 (2.174–5.000)	5	157/105
Ikeda et al ²⁷	2003	Japan	356 (327/29)	C/R + S + C/R	OS	SCC + AC + OT	1.52 (1.05–2.21)	5	186/170
Shimada et al ²⁸	2003	Japan	150 (128/22)	S	OS	SCC	1.42 (0.83–2.41)	10	67/83
Gockel et al ²⁹	2006	Germany	291 (NA)	S	OS	SCC + AC + OT	1.182 (1.030–1.356)	5	NA
Wang et al ³⁰	2009	Taiwan	123 (120/3)	R	OS	SCC + AC	12.116 (3.449–42.567)	5	22/101
Zingg et al ³¹	2010	Australia	90 (74/16)	C/R + S	OS	SCC + AC	1.42 (0.71–2.85)	10	75/15
Feng et al ³²	2013	People's Republic of China	43 (30/13)	S + C/R	OS	SCCE	2.756 (1.115–6.813)	10	NA
Song et al ³³	2013	People's Republic of China	156 (134/22)	S + C/R	OS	SCC	2.131 (1.213–4.451)	5	NA

Abbreviations: M/F, male/female; S, surgery; C/R, chemotherapy/radiotherapy; R, radiotherapy; OS, overall survival; SCC, squamous cell carcinoma; AC, adenocarcinoma; OT, others; SCCE, small cell carcinoma of the esophagus; NA, not available; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis.

In the subgroup analyses, with data stratified by treatment and pathological type, both subgroups showed significant HRs and 95% CIs. These results, on the other hand, indicated that no matter what treatment or pathological type the patients were in, the high levels of serum CRP could significantly predict the poor OS in patients with EC. In addition, when stratified by cut-off value, the results were also significant no matter what cut-off level was used: 5 mg/L (HR: 1.38, 95% CI: 1.22–1.56, $P=88.6\%$) or 10 mg/L (HR: 1.60, 95% CI: 1.09–2.35, $P=0$).

The molecular mechanism by which CRP can be correlated with a prognosis of cancer remains to be determined. One possible explanation is interleukin-6 (IL-6). CRP is synthesized mainly by hepatocytes.^{12,13} Production of CRP by hepatocytes is induced mainly by IL-6, although other cytokines, such as tumor necrosis factor α (TNF α), transforming growth factor β (TGF β), and IL-1, can also synthesize this protein.^{35,36} It has been reported that IL-6 is able to contribute to the cancer growth and progression.^{37,38} Moreover, IL-6 probably links the inflammation and

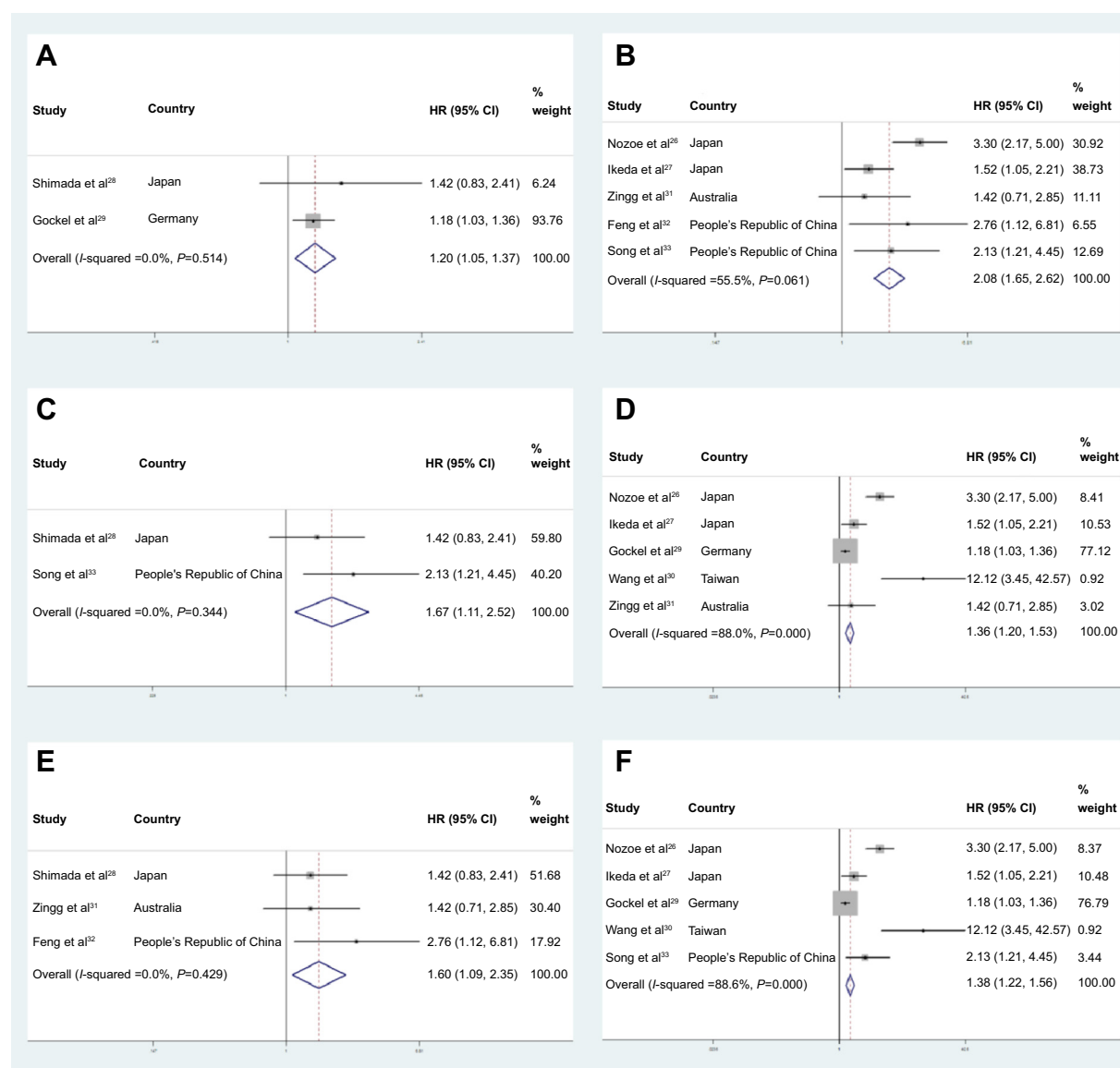
**Figure 2** Forest plot of the association between serum CRP and OS in EC.

Abbreviations: CRP, C-reactive protein; OS, overall survival; EC, esophageal cancer; HR, hazard ratio; CI, confidence interval.

Table 2 Subgroup analyses of pooled HRs for increased serum CRP and OS in EC

Subgroup	Number of cohorts	Number of patients	References	HR (95% CI)	Heterogeneity	
					I^2 (%)	P-value
Treatment						
S	2	441	28, 29	1.20 (1.05–1.37)	0.0	0.514
S + AT	5	907	26, 27, 31, 32, 33	2.08 (1.65–2.62)	55.5	0.061
Pathological type						
SCC	2	306	28, 33	1.67 (1.11–2.52)	0.0	0.344
SCC + AC/OT	5	1,122	26, 27, 29, 30, 31	1.36 (1.20–1.53)	88.0	<0.0001
Cut-off level						
5 mg/L	5	1,188	19, 20, 23, 24, 27	1.38 (1.22–1.56)	88.6	<0.0001
10 mg/L	3	283	22, 25, 26	1.60 (1.09–2.35)	0.0	0.429

Abbreviations: S, surgery; AT, adjuvant therapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; OT, others; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; OS, overall survival; EC, esophageal cancer.

**Figure 3** Forest plot of the association between serum CRP and OS in EC by subgroup analyses.

Notes: Subgroup analysis according to treatment (**A**) surgery only; (**B**) surgery combined with chemotherapy/radiotherapy, pathological type; (**C**) squamous cell carcinoma; (**D**) squamous cell carcinoma, adenocarcinoma and others and cut-off level (**E**) cut-off = 10 mg/L; (**F**) cut-off = 5 mg/L.

Abbreviations: CRP, C-reactive protein; OS, overall survival; EC, esophageal cancer; HR, hazard ratio; CI, confidence interval.

angiogenesis via the expression of vascular endothelial growth factor (VEGF).³⁹ On the other hand, as with other proteic biomarkers of SIR, CRP has several biological functions, including complement activation and platelet activation.^{40,41}

There are several limitations in our meta-analysis. First, the number of included studies was limited. Second, significant heterogeneity was observed. Third, the pooled predictive HR between serum CRP and OS were not strong (HR=1.40, $P<0.0001$). Empirically, HR>2 is considered strongly predictive.⁴² Therefore, the results should be used with caution when using CRP to predict OS in EC. Moreover, our meta-analysis showed that CRP is an independent predictive factor in patients with EC; however, it should be kept in mind that CRP alone, without other variables, may not be associated with postoperative survival in patients with EC. In addition, in our study, variation in the types of treatment may have had an influence on OS, and this can possibly introduce bias into the study. The results should therefore be interpreted with caution. Further large prospective studies should be performed to confirm whether serum CRP has a prognostic value in patients with EC.

In conclusion, our meta-analysis revealed that high levels of serum CRP were significantly associated with poor OS in patients with EC. We conclude that serum CRP might serve as a useful biomarker for EC.

Disclosure

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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