Preoperative elevation of serum C-reactive protein as an indicator of poor prognosis for early-stage esophageal squamous cell carcinoma

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Abstract Preoperative elevation of serum C-reactive protein (CRP) is reportedly associated with poor prognosis in several types of cancer. This study investigated the role of serum CRP as a prognostic factor in early-stage esophageal squamous cell carcinoma (ESCC). The preoperative serum CRP levels were measured in 156 newly diagnosed pT1–2N0M0 patients using an enzyme-linked immunosorbent assay. Correlations between serum CRP levels and other clinical parameters were analyzed. Multivariate analyses were performed to find prognostic markers using Cox's proportional hazards model. CRP concentrations were within the normal range in 117 (75%) individuals, but were elevated in 39 (25%) patients. Serum CRP levels were significantly correlated with the tumor length (p = 0.032), depth (T classification, p = 0.0157), or histologic grade (p = 0.034). The overall 5-year survival rates were 76.3% and 50.2% in the low- and high-CRP groups, respectively (p = 0.005). By multivariate analyses, the elevated serum CRP level was found to be an independent prognostic factor for poor survival (hazard ratio = 2.131; p = 0.007), regardless of tumor classification or other prognostic factors. In conclusion, preoperative, high serum CRP is an independent determinant of poor prognosis in early-stage ESCC.

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Introduction

C-reactive protein (CRP), generally produced by hepatocytes, is an acute-phase protein, whose levels increase in various inflammatory conditions [1]. Furthermore, CRP has been reported as a predictor of survival in different malignancies, including pancreatic [2], ovarian [3], pulmonary [4], and colorectal [5] cancers. However, its role in early-stage esophageal squamous cell carcinoma (ESCC) has not been characterized well. In this study, we aimed to investigate the relationship between the preoperative elevation of serum CRP level and clinical features of early-stage ESCC and to establish its possible role as a prognostic marker for ESCC patients.

Patients and methods

The study participants comprised 156 patients who underwent curative resection of ESCC in our department between January 2004 and July 2010. Patients with inflammatory conditions, including infections or collagen diseases, and those with primary cancers in other organs, all of which possibly influence the serum CRP levels, were excluded. The patients who did not die of disease progression were excluded from our study. No study patient had received induction chemotherapy or radiotherapy. The tumor-node-metastasis (TNM)-stage classification was assessed according to the 2009 American Joint Committee on Cancer (AJCC) staging system [6]. Preoperative evaluations and staging workups included recording patients’ medical histories, physical examinations, complete blood cell counts, serum biochemistry tests, thoracic computed tomography (CT), upper abdominal ultrasounds, magnetic resonance brain imaging, entire body bone scans, and positron emission tomography (PET) scans (partly with PET/CT). All patients were confirmed by pathological T1 or T2 signals without lymph-node metastases after surgery.

Measurement of serum CRP

Serum was collected 1 day prior to the operation to measure the CRP level, which was determined once for each patient. Serum CRP was measured using a CRP ELISA (enzyme-linked immunosorbent assay) kit (Westtang Corporation, Shanghai, China). The normal serum CRP range is 0–5 mg/L. Hence, a serum CRP concentration of >5 mg/L was considered positive.

Patient follow-up

Surviving patients were followed-up every 3–6 months for the first 5 years, and then once annually. Each patient’s history, physical examination, and thoracic CT scans were recorded at each follow-up session. Survival time was recorded from the 1st day of operation to the date of death or the last follow-up visit. July 1, 2011 was the last censoring date for survival. The median survival time from surgery to the last censoring date was 56 months (range, 12–84 months).

Statistical analysis

The Chi-square test was used to compare the data. Survival curves were generated using the Kaplan–Meier method from the start of confirmed pathology to the date of death or last follow-up. Multivariate analysis was performed using the Cox regression model. Statistical analysis was performed with the SPSS version 16 software (SPSS Inc., Chicago, IL, USA). Confidence intervals were calculated at the 95% level (95% CI). Follow-up extended through January 1, 2012.

Results

A total of 156 patients, including 134 men and 22 women (median age, 59 years; range, 31–78 years) were enrolled in our study. Patients’ tumors were histologically confirmed to be ESCC. Tumors were located in the upper third in 10 (6.4%) patients, in the middle third in 82 (52.6%) patients, and in the lower third of the esophagus in 64 (41%) patients. In total, 112 individuals (71.8%) underwent Ivor-Lewis esophageal resection, and 44 individuals underwent tri-incisional esophageal resection or other surgical procedures. The average number of resected lymph nodes was 24.9 (range, 12–72). Thirty-nine and 116 patients underwent three- and two-field lymph-node dissections, respectively. Serum CRP levels were higher than 5 mg/L in 39 patients and lower than 5 mg/L in 117 patients. Median CRP levels were 3.9 (95% CI, 3.6–4.1) and 21.2 (95% CI, 13.1–41.2) in the low- and high-CRP groups, respectively. Table 1 shows the relationship between serum elevation of CRP and clinicopathological characteristics of study patients. Significant differences were found in the tumor length (p = 0.032), depth of tumor invasion (p = 0.0157), and histological tumor grading (p = 0.034).

Factors affecting overall survival by univariate and multivariate analyses

Univariate analyses were performed using the Kaplan–Meier method to assess the predictive capacity of each tested variable (Table 2). Pathologic T classification (p = 0.029), tumor length (p = 0.043), and CRP levels (p = 0.005) were predictive of survival.

As Fig. 1A demonstrates, there was a significant difference in survival time between the low- and high-CRP group (the 5-year survival rates were 76.3% and 50.2% in the low- and high-CRP groups, respectively; p = 0.005). The 5-year disease-free survival rates were 60.4% and 40.5% in the low- and high-CRP groups, respectively (p = 0.036; Fig. 1B). There was a significant difference in survival time between the low- and high-CRP groups with T1 and T2 classification patients (Fig. 2A and B).

A multivariate Cox’s regression model was constructed considering age, sex, T status, histologic grade, tumor location, tumor length (<3 cm vs. ≥3 cm), serum albumin level (SAL), and CRP levels as variables. T status and CRP level qualified as independent prognostic factors (Table 3).
Other factors affecting overall survival

The data of postoperative CRP were collected from 67 patients within 6 months after surgery. The difference in survival rates between the groups with high and low CRP levels was statistically significant. The overall 5-year survival rates were 90.6% and 63.6% for the low- and high-CRP groups, respectively (p = 0.043; Fig. 3). Based on the preoperative SALs in all 156 patients, the overall 5-year survival rates were found to be 70.1% and 52.9% in normal- and low-SAL groups, respectively (p = 0.057).

Discussion

To the best of our knowledge, this is the first study evaluating the clinical significance of serum CRP levels in predicting survival in early-stage ESCC patients. Multivariate analyses showed preoperative serum CRP along with pathologic T status to be significant, independent prognostic markers for ESCC.

Previous studies have reported elevation of preoperative serum CRP levels as a significant prognostic parameter in patients with some carcinomas [2–10]. Mechanisms underlying CRP elevation are well known. Production of CRP by liver is strongly induced by cytokines including interleukin-1, interleukin-6, and tumor-necrosis factor [11–13]. Interleukin-6 is highly expressed by various tumor cells. For example, studies using esophageal cancer cell lines or esophageal surgical specimens have shown that some types of esophageal carcinomas produce interleukin-6 [14]. Similar to other proteinaceous markers of acute inflammation, CRP has several biological roles including opsonization, chemotaxis, platelet activation, and complement activation by the classical pathway [15]. Recent studies suggest that CRP functions as a primitive immunoglobulin by binding to the Fc fragment of immunoglobulins or to several pathogenic microorganisms [16]. This role of CRP underlying antitumor immunity apparently correlates with poor prognosis in carcinomas.

Previously, an elevated serum CRP level was associated with reduced progression-free patient survival or overall survival independent of other clinically established prognosticators [17,18]. CRP is reported to be associated with a negative chemotherapy and radiotherapy response factor. However, the role of CRP in early-stage ESCC has not been examined until now. In this study, we found high serum CRP level as a determinant of poor prognosis in early-stage ESCC; the 5-year survival rate was lower in patients with
higher CRP levels than in patients with lower CRP levels (50.2% vs. 76.3%; \( p = 0.005 \)).

According to the guidelines of the National Comprehensive Cancer Network, systemic chemotherapy is not recommended in early-stage ESCC. The PT1–2 status without any lymph-node metastases was a desirable outcome after complete tumor resection. However, the 5-year survival time was not favorable. The high-risk factor in such cases is not well studied in the clinic. Our results suggest that CRP level may be a useful indicator for defining a subset of early-stage ESCC patients with unfavorable prognoses and, thus, requiring intensive treatment. Patients with high preoperative CRP in the early-stage of the disease may require intensive systemic chemotherapy compared to those with low CRP levels.

Measurement and quantification of serum CRP levels are relatively inexpensive and easy in clinical practice. Preoperative serum CRP levels can be determined easily in patients with esophageal cancers. Accordingly, serum CRP, as

![Figure 1](image1.png)

**Figure 1.** (A) Overall survival in patients with low versus high preoperative CRP levels (\( p = 0.005 \)). (B) Disease-free survival in patients with low versus high preoperative CRP levels (\( p = 0.036 \)). CRP = C-reactive protein.

![Figure 2](image2.png)

**Figure 2.** (A) Overall survival in T1 classification patients with low versus high preoperative CRP levels (\( p = 0.047 \)). (B) Overall survival in T2 classification patients with low versus high preoperative CRP levels (\( p = 0.003 \)). CRP = C-reactive protein.

### Table 3  Factors associated with the prognosis of patients with esophageal squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% CI</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.862</td>
<td>0.392–1.895</td>
<td>0.711</td>
</tr>
<tr>
<td>Age</td>
<td>0.712</td>
<td>0.389–1.571</td>
<td>0.576</td>
</tr>
<tr>
<td>Tumor classification</td>
<td>1.921</td>
<td>1.331–2.917</td>
<td>0.041</td>
</tr>
<tr>
<td>Tumor length</td>
<td>0.521</td>
<td>0.417–1.251</td>
<td>0.194</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>1.175</td>
<td>0.694–1.994</td>
<td>0.558</td>
</tr>
<tr>
<td>Tumor location</td>
<td>1.351</td>
<td>0.573–2.156</td>
<td>0.617</td>
</tr>
<tr>
<td>CRP level</td>
<td>2.131</td>
<td>1.213–4.451</td>
<td>0.007</td>
</tr>
<tr>
<td>SAL</td>
<td>1.535</td>
<td>0.989–2.135</td>
<td>0.097</td>
</tr>
</tbody>
</table>

CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; SAL = serum albumin level.
a significant prognosticator, can be used with other conventional staging methods to predict survival in patients with early-stage ESCC.

In conclusion, we suggest that preoperative serum CRP can be used as a prognostic factor in early-stage ESCC patients. High CRP levels indicate poor prognoses by reducing the overall survival times of patients; moreover, they are likely to complement the prognostic role of TNM staging. This study had inherent limitations because of its retrospective nature; hence, the association between CRP level and survival outcome should be investigated further.

References