Prognostic Significance of C-reactive Protein in Urological Cancers: a Systematic Review and Meta-analysis

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Abstract

Background: C-reactive protein (CRP), considered as a prototypical inflammatory cytokine, has been proposed to be involved in tumor progression through inflammation. Recent studies have indicated CRP as a prognostic predictor for urological cancers, but the results remain controversial. Materials and Methods: A systematic search of Medline, Scopus and the Cochrane Library was performed to identify eligible studies published between Jan 1, 2001 and Sep 1, 2013. Outcomes of interest were collected from studies comparing overall survival (OS), cancer-specific survival (CSS) and relapse-free survival (RFS) in patients with elevated CRP levels and those having lower levels. Studies were pooled, and combined hazard ratio (HR) of CRP with its 95% confidence interval (CI) for survival were used for the effect size estimate. Results: A total of 43 studies (7,490 patients) were included in this meta-analysis (25 for RCC, 10 for UC, and 8 for PC). Our pooled results showed that elevated serum CRP level was associated with poor OS (HR: 1.26, 95% CI: 1.22-1.30) and RFS (HR: 1.38, 95% CI: 1.29-1.47), respectively. For CSS the pooled HR (HR: 1.33, 95% CI: 1.28-1.39) for higher CRP expression could strongly predict poorer survival in urological cancers. Simultaneously, elevated serum CRP was also significantly associated with poor prognosis in the subgroup analysis. Conclusions: Our pooled results demonstrate that a high serum level of CRP as an inflammation biomarker denotes a poor prognosis of patients with urological cancers. Further large prospective studies should be performed to confirm whether CRP, as a biomarker of inflammation, has a prognostic role in urological cancer progression.

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

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Introduction

Systemic inflammation plays an important role in various aspects of cancer involving cancer initiation, promotion, progression, metastasis and clinical features (Mantovani et al., 2008) and cancer-related inflammation has been recognized as the seventh hallmark of cancer (Colotta et al., 2009). Based on increasing evidence of the association between cancer-related inflammation and the progression of cancer, the external symptoms of systemic inflammatory response has been shown to be indicative of poor prognosis in many malignancies (Guo et al., 2013; Yu et al., 2013), including urological cancers. C-reactive protein (CRP), a representative acute-phase reactant, is a significant and sensitive inflammatory marker that can be objectively measured using reliable assays in clinical practice. CRP has been shown to be significant in the prediction of outcomes of urological cancers, including renal cell carcinoma (RCC), upper urinary tract and bladder cancers (UC), and prostate cancer (PC). The elevation of C-reactive protein levels, which indicate the presence of cancer-associated systemic inflammatory response, is linked to poorer survival in patients with urological cancers, including renal cell carcinoma, upper urinary tract and bladder cancers, and prostate cancer. With this strong prognostic ability, C-reactive protein can be incorporated into prognostic models and will make them simpler and improve their predictive accuracy. As such, C-reactive protein can be used to monitor treatment efficacy and disease course using serial measurements. Taken together, these findings show that C-reactive protein can act as an important biomarker for urological cancers. However, as a matter of contradictory results as well as the small sample size in solitary study, the current opinion of CRP as the prognostic biomarker in urological cancers is still controversial. In the present study, we attempt to conduct a systematic review and meta-analysis to estimate the prognostic significance of elevated serum CRP levels for overall survival (OS) cancer special survival (CSS) and recurrence-free survival (RFS) on the basis of the currently available evidence in urological cancers, including RCC, UC and PC.
Materials and Methods

Literature search and study selection

A systematic search of the electronic databases, including Medline, Scopus and Cochrane Library was performed to identify original articles published from 2001 up to Sep 1, 2013 focusing on the prognostic impact of CRP in urological cancers using the following terms: “C-reactive protein”, “renal cell carcinoma”, “upper tract”, “bladder cancer” and “prostate cancer”. All selected papers were full-text English language articles. In addition, the reference lists of identified articles were also searched for further relevant articles.

Inclusion criteria and exclusion criteria

Studies were considered eligible if they met the following criteria: (1) they measured preoperative serum CRP values; (2) they evaluated the potential association between preoperative CRP level and the survival outcome of urological cancers; (3) and their study was retrospective or prospective in design. Articles were excluded based on the following criteria: (1) review articles or letters, (2) non-English articles, (3) laboratory studies and (4) non-human research.

Data extraction and outcomes of interest

Two reviewers (J.D & K.T) extracted independently the following data including: first author, year of publication, country, study design, disease, No. of patients, treatment, cut off of CRP, outcomes of interest and follow-up time. All disagreements about eligibility were resolved by a third reviewer (H.X) by discussion until a consensus was reached. Our outcomes of interest were OS, CSS and RFS.

HR pooled and meta-analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the impact of targeted therapies on OS, CSS and RFS. A combined HR>1 implied a worse survival, and it was considered statistically significant if 95%CI for the combined HR did not overlap 1. For the studies in which HR was not given directly, the published data and figures from original papers were used to calculate the HR according to the methods described by Parmar et al (Parmar et al., 1998). The O-E and variance were calculated from the reported data directly by HR and its 95%CI or indirectly by log-rank \( p \) value with number of events, or data reading from Kaplan-Meier survival curve. All \( p \) values are two-tailed with a significant level at 0.05. Kaplan-Meier curves were read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) (Tierney et al., 2007). This work was performed by two independent persons to reduce inaccuracy in the extracted survival rates.

We performed the meta-analysis by using the Review Manager Software (RevMan 5.1, Cochrane Collaboration, Oxford, UK). \( \chi^2 \) and \( I^2 \) statistics were used directly to examine the heterogeneity between each study. By heterogeneity test, if \( p > 0.05 \), we select the fixed-effect model, and if not, a random-effect model was used. We used HR and its CI to evaluate the association between the elevated CRP level and survival in urological cancers.

Results

Characteristics of included studies

A total of 43 eligible studies (7, 490 patients) were identified for this meta-analysis (25 for RCC (Atzpodien et al., 2003; Bromwich et al., 2004; Casamassima et al., 2005; Peccatori et al., 2005; Ito et al., 2006; Lamb et al., 2006; Vogl et al., 2006; Karakiewicz et al., 2007; Komai et al., 2007; Ramsey et al., 2007; Kawata et al., 2008; Ramsey et al., 2008; Tanaka et al., 2008; Imura et al., 2009; Miyake et al., 2009; Jagdev et al., 2010; Cho et al., 2011; Falkensammer et al., 2011; Ito et al., 2011; Bedke et al., 2012; Fujita et al., 2012; Sim et al., 2012; Steffens et al., 2012; de Martino et al., 2013; Yasuda et al., 2013), 10 for UC (Hilmy et al., 2005; Hilmy et al., 2006; Saito et al., 2007; Yoshida et al., 2008; Gakis et al., 2011; Saito and Kihara, 2011; Ishioka et al., 2012; Obata et al., 2012; Tanaka et al., 2012; Stein et al., 2013), and 8 for PC (McArule et al., 2006; Beer et al., 2008; Nakashima et al., 2008; McArule et al., 2010; Ito et al., 2011; Pond et al., 2012; Prins et al., 2012; Hall et al., 2013)) (Figure 1). First author, year of publication, country, study design, disease, No. of patients, treatment, cut off of CRP, follow-up time and outcomes of interest including OS, CSS, RFS and pooled HR were extracted individually from each study and listed Table 1.

The association between serum CRP level and urological cancers prognosis

19, 23, 13 studies reported elevated CRP with OS, CSS and RFS respectively. Our pooled results showed that elevated serum CRP level was associated with poor OS (HR: 1.26, 95%CI: 1.22-1.30; Figure 2) and RFS (HR: 1.38 95%CI: 1.29-1.47; Figure 3), respectively. For CSS the pooled HR (HR: 1.33, 95%CI: 1.28-1.39; Figure 4) in higher CRP expression which could strongly predict poorer survival in urological cancers. There was significant heterogeneity for OS (\( I^2=90\% \)), CSS (\( I^2=86\% \)) and RFS (\( I^2=84\% \)).

Subgroup analysis

In the further investigation, subgroup analyses were performed to evaluate whether the pooled HR for OS, CSS and RFS were different according to matching. When the
Table 1. Characteristics of Eligible Studies

| Reference          | Country | Design | Disease          | No. of patients | Treatment                                      | Cut off of CRP (mg/L) | Survival | HR (95% CI) | Follow-up months* |
|--------------------|---------|--------|------------------|-----------------|------------------------------------------------|----------------------|----------|-------------|------------------|
| Aitzpodien, 2003   | Germany | CC-RCC | Nephrectomy      | 11              | OS 50.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 20 (0-157)    |
| Bedele, 2012       | Germany | MRCC   | Nephrectomy      | 125             | OS 75.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 30 (10-157)    |
| Broome, 2004       | Italy   | MRCC   | Nephrectomy      | 10              | OS 15.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 40 (10-157)    |
| Casamassima, 2005  | Italy   | MRCC   | Nephrectomy      | 10              | OS 25.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 50 (10-157)    |
| Cho, 2011          | Korea   | MRCC   | Nephrectomy      | 10              | OS 30.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 60 (10-157)    |
| Fulkensammer, 2010 | Austria | MRCC   | Nephrectomy      | 10              | OS 40.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 70 (10-157)    |
| Fujita, 2012       | Japan   | RCC    | Nephrectomy      | 10              | OS 50.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 80 (10-157)    |
| Imura, 2009        | Japan   | CC-RCC | Nephrectomy      | 10              | OS 15.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 90 (10-157)    |
| Ito, 2006          | Japan   | RCC    | Nephrectomy      | 10              | OS 25.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 100 (10-157)   |
| McArdle, 2010      | UK      | LPC    | Nephrectomy      | 10              | OS 30.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 110 (10-157)   |
| McArdle, 2006      | UK      | MCRPC  | Nephrectomy      | 10              | OS 40.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 120 (10-157)   |
| Pond, 2012         | UK      | RCC    | Nephrectomy      | 10              | OS 50.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 130 (10-157)   |
| Yoshida, 2008      | Japan   | RCC    | Nephrectomy      | 10              | OS 60.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 140 (10-157)   |
| Hall, 2013         | USA     | RCC    | Nephrectomy      | 10              | OS 70.00 (1.37 4.15)                              | 1.00 (0.99-1.00)     | 1.10 (1.05-1.16) | 150 (10-157)   |

Discussion

CRP is a representative acute-phase reactant and is the most widely used marker of inflammation, as it is cost-effective and non-invasive (Saito and Kihara, 2010). An increasing number of studies have shown that CRP is a significant prognostic factor for metastasis and mortality.
in urological cancers. The prognosis for patients with elevated CRP concentration is poor. The underlying inflammatory process related to cancer plays an important role in the progression of renal cell carcinoma (Saito and Kihara, 2013). On the one hand, immunotherapy, relying on the host mounting a cytotoxic immune response to the tumor, has shown a survival advantage for men with advanced prostate cancer. On the other hand, systemic inflammation may create a pro-tumor environment and portend a poor prognosis (Saito and Kihara, 2011).

The objective of our meta-analysis was to examine the association between elevated serum CRP level and survival in patients with urological cancers. This meta-analysis combined the results from 43 studies of 7,490 patients and revealed that high CRP level significantly predicted poor OS (HR: 1.26), CSS (HR: 1.33) and RFS (HR: 1.38) of urological cancers patients which are consistent with previous studies.

In urological cancer, the importance of CRP as a potential biomarker has been investigated most intensively in RCC (Saito and Kihara, 2010). Numerous studies have shown that CRP is a significant prognostic factor for RCC patients treated with surgery and/or systemic therapy. Our evidence demonstrates CRP is associated with poor prognosis of RCC which is consistent with a previous meta-analysis study (Wu et al., 2011). The prognostic significance of CRP has been shown with its power for overall survival in patients with RCC. Furthermore, it has been suggested that CRP may serve as a marker for monitoring disease activity and response to therapy in patients with RCC.

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**Figure 2. Forest Plots of Hazard Ratios for C-Reactive Protein (CRP) in Patients with Urological Cancers Overall Survival (OS)**

![Forest Plots of Hazard Ratios for C-Reactive Protein (CRP) in Patients with Urological Cancers Overall Survival (OS)](image)

**Table 2. Subgroup Analysis**

| Subgroup | OS | CSS | RFS |
|----------|----|-----|-----|
| Overall  | 1.26 [1.22, 1.30] | 1.33 [1.28, 1.39] | 1.38 [1.29, 1.47] |
| Disease  | 1.26 [1.21, 1.31] | 1.34 [1.27, 1.41] | 1.34 [1.24, 1.44] |
| UC       | 1.63 [1.33, 1.99] | 1.31 [1.21, 1.41] | 1.56 [1.25, 1.96] |
| PC       | 1.22 [1.14, 1.30] | 1.90 [1.32, 2.75] | 1.48 [1.27, 1.72] |
| Area     | 1.29 [1.23, 1.34] | 1.29 [1.24, 1.35] | 1.30 [1.21, 1.41] |
| Asian    | 1.26 [1.16, 1.36] | 2.39 [2.00, 2.86] | 1.81 [1.48, 2.22] |
| America  | 1.20 [1.12, 1.29] | / | 1.48 [1.27, 1.72] |
| Design   | Prospective | 1.24 [1.19, 1.28] | 1.29 [1.23, 1.36] | 1.34 [1.25, 1.43] |
| Retrospective | 1.35 [1.26, 1.45] | 1.42 [1.32, 1.53] | 1.76 [1.45, 2.13] |
| Sample   | >110 | 1.25 [1.21, 1.30] | 1.30 [1.25, 1.36] | 1.35 [1.27, 1.44] |
| ≤110     | 1.30 [1.21, 1.41] | 2.17 [1.79, 2.63] | 2.84 [1.87, 4.31] |

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**Figure 3. Forest Plots of Hazard Ratios for C-Reactive Protein (CRP) in Patients with Urological Cancers Recurrence Failure Survival (RFS)**

**Figure 4. Forest Plots of Hazard Ratios for C-Reactive Protein (CRP) in Patients with Urological Cancers Cancer-Special Survival (CSS)**

![Forest Plots of Hazard Ratios for C-Reactive Protein (CRP) in Patients with Urological Cancers Cancer-Special Survival (CSS)](image)
improving the combined predictive accuracy. Karakiewicz et al. reported CRP improved the predictive accuracy by 3.7% for CSS including 313 patients with any stage of RCC (Karakiewicz et al., 2007). And this prognostic effect for survival not only significant in localized but also in advanced metastatic RCC. In addition to nephrectomy studies, CRP is also a prognostic marker for MRCC patients receiving systemic cytokine therapy (IFN-a and/or IL-2). Patients with high CRP level (>50 mg/L) had an increased risk of cancer progression during IL-2 therapy than those without. Miyake et al. showed that pretreatment CRP levels also had a significant impact on the response to receiving IL-2 and INF-a combination therapy (Miyake et al., 2009).

The current evidence indicates CRP as a biomarker that satisfies the NIH criteria for UC. Moreover, elevated pretreatment CRP level was associated with a poor CSS after treatment with chemoradiotherapy in 88 patients with MIBC (Yoshida et al., 2008). In this study, multivariate analysis showed that CRP and cT stage were independent prognostic indicators for CSS, with a HR of 1.80 (1.01-2.97). Furthermore, post-treatment CRP status still provided additional information for prognosis. Based on the significance of CRP in predicting the prognosis for UC, Gakis et al proposed a new prognostic algorithm TNR-C (tumor stage, lymph node density, resection margin status and the presence or absence of elevated CRP level) incorporating CRP levels for invasive bladder cancer (Gakis et al., 2011). They conducted 246 patients with bladder cancer who underwent radical cystectomy which demonstrated a statistically significant enhancement of predictive accuracy (by 4.9%) by adding CRP to a basic prognostic model encompassing major pathological parameters of survival (Gakis et al., 2011).

Our data also demonstrated CRP as a prognostic factor in prostate cancer. CRP was highly correlated with prostate cancer patients who had bone metastasis than those without metastasis (Lehrer et al., 2005). Nakashima et al. showed that CRP, as well as the extent of disease on bone scan, is an independent prognostic factor for prostate cancer with bone metastasis (Nakashima et al., 2008). Elevation of CRP level (>1.5 mg/L) was associated with poor survival in 126 patients (HR 1.88), as well as the extent of disease of bone metastasis (extent of disease 2 or greater, HR 2.24). However, in a large sample study found no association between CRP level and risk of prostate cancer (Van Hemelrijck et al., 2011). In the advanced CRPC, because of the reduced prognostic power of PSA, CRP might become more significant as a prognosis predictor. Two phase II clinical trials including docetaxel in the treatment reported the significance of CRP as a prognostic indicator. In the trial patients with metastatic CRPC were given docetaxel, CRP levels were elevated in 102 patients and CRP was an independent prognostic factor for OS as both continuous (HR 1.41) and categorical (cut-off point: 8 mg/L, HR 2.96) variables. The other trial in patients with CRPC reported that elevated serum CRP of 5 mg/L was associated with poor OS (HR 1.11). Ito et al also demonstrated that CRP was an independent prognostic factor for CRPC treated with docetaxel (cut-off 5 mg/L, HR 1.95).

Notably, we should admit that there existed certain inherent limitations in the trials included in our meta-analysis that cannot be ignored when interpreting our data. The major limitation is that our findings are based on the limitations of the included studies. Second, here we performed only in the three most common urological cancers, thus prostate cancer, renal cell carcinoma and bladder cancer, while testis and penis carcinoma were excluded. Third, significant heterogeneity was observed because of methodological and demographic differences among studies examining CRP and prognosis in urological cancers. The cut-off values of CRP varied greatly between the studies may be the main reason for this heterogeneity. We used appropriate well-motivated inclusion criteria to maximize homogeneity, and performed subgroup analyses to investigate potential sources of heterogeneity. Moreover, the pooled predictive of CRP for survival, although statistically significant, were not strong, with global HRs of 1.22, 1.38 and 1.36, respectively. Empirically, HR>2 is considered strongly predictive (Hayes et al., 2001). Hence, caution be taken when using CRP to predict urological cancers survival because of the lower power in HRs. Last, our meta-analysis does not provide evidence on the additional value of serum CRP measurements to the discrimination already attained by clinical variables, or on whether measurement of CRP may alter the clinical management of urological cancers. Such questions could be answered in further well designed robust large sampleRCTs. However, this systematic review and meta-analysis was conducted at an appropriate time with enough data available for extraction by a comprehensive and robust search strategy. Also, we applied a rigorous inclusion/exclusion criterion, different subgroups to identify studies, fully outcomes of interest (OS, CSS, and RFS) and advanced meta-analysis of HR for survival. Here, we provide up-to-date information of prognostic significant role of serum CRP level in urological cancers which may worth reference on the clinical decision.

In conclusion, CRP as a role of representative cost-effective and non-invasive biomarker for systemic inflammatory response has a significant impact in predicting outcomes of urological cancer. Our meta-analysis suggests that elevated CRP is associated with poor prognosis in urological cancers which indicated that inflammation is involved in the pathogenesis of cancer progression. These findings allow us to conclude that CRP might serve as a useful biomarker of disease outcome for urological cancers and it is already measured objectively and affordably in clinical practice worldwide. Furthermore, the CRP kinetics of dynamic changes in CRP levels can be used to monitor the disease course, such as the effect of treatment intervention or further progression. Our meta-analysis has provided a better understanding of the association between the presence of systemic inflammatory response and cancer progression, and novel anti-inflammatory therapies that target the tumor microenvironment might also be considered in the future. However, further large prospective studies should be performed to confirm whether CRP, as a biomarker of inflammation, has a prognostic role in urological cancers progression.
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