Pooled Analysis of C-Reactive Protein Levels and Mortality in Prostate Cancer Patients

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Abstract

This was a pooled analysis of studies on C-reactive protein (CRP) and prostate cancer mortality. Two hundred thirty-five patients were included. CRP was significantly associated with mortality; the best predictor cutoff was CRP < 12 mg/L. CRP is a routine assay that could be tested at diagnosis to improve prognostication of prostate cancer patients.

Introduction: Previous studies have reported that higher C-reactive protein (CRP) levels are significantly associated with worse outcome in prostate cancer patients. The size of each individual study was not large enough to allow sufficient statistical power to draw conclusions. We conducted a pooled analysis of individual data of published studies to evaluate the association between increased CRP level and risk of death in prostate cancer, and to find the best CRP cutoff that could predict mortality. **Materials and Methods:** Original research studies on prostate cancer survival and CRP levels were identified (n = 6). Corresponding authors were contacted and invited to share individual data. Two data sets were received (235 patients). The combined hazard ratio (HR) was calculated and adjusted for age, prostate-specific antigen, hemoglobin, and alkaline phosphatase. The best cutoff of CRP was explored using X-title software version 3.6.1. **Results:** High CRP level was statistically significantly associated with mortality (meta-HR, 1.83 [95% confidence interval (CI), 1.51-2.21]), without evidence of heterogeneity among studies. At pooled analysis, adjusted pooled HR for CRP $<$ 5 versus $\geq$ 5 mg/L was 1.44 (95% CI, 1.02-20.4). The best CRP cutoff was 12 mg/L: the adjusted HR_{pooled} for CRP $<$ 12 versus $\geq$ 12 mg/L was 1.53 (95% CI, 1.01-2.32). **Conclusion:** Increased CRP levels are associated with overall survival in prostate cancer patients. Because CRP is an affordable and readily available assay, it might hold promise in improving prognostication and potentially to predict the activity of specific therapeutic agents.

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Introduction

Prostate cancer is the most common cancer and the second leading cause of cancer death in men in the United States.[1] Despite the fact that most prostate cancers are diagnosed when they are still localized, as many as 30% of the cases will recur after an attempt at cure. Biochemically relapsed or metastatic prostate cancer is initially controlled by androgen suppression therapy. However, the cancer eventually becomes resistant to these maneuvers and is frequently lethal.

Much effort has been put into finding suitable predictive markers that could help distinguish those prostate cancer cases that will become more aggressive and will likely recur after treatment from tumors that are more indolent, in which a conservative management approach would be preferred to avoid overtreatment.[2] Challenges exist in the management of advanced disease, in which the clinical phenotype is heterogeneous, the ability to predict subsequent natural history is limited, and therapy choices are hampered by these knowledge gaps. Predictive biomarkers in this area are needed.

Epidemiologic evidence has linked prostate cancer occurrence to chronic inflammation-causing factors such as infectious agents, chronic and persistent infections, proinflammatory, hormonal, or dietary factors.[3,4] In some studies, chronic use of anti-inflammatory agents has been associated with a protective effect against prostate cancer.[5] Inflammatory factors might also lead to resistance to therapy in advanced disease.

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Increased C-reactive protein (CRP) level, one of the most common and routinely measured markers of systemic inflammation, has been associated with the risk of developing specific cancers,[6] such as colorectal and lung cancer,[7,8] and it has been associated with a poor prognosis for overall cancer and specifically for breast, lung, gastric, and colorectal cancer, and renal cell carcinoma.[9,10]

Previous studies have reported that higher CRP levels are significantly associated with worse outcome in prostate cancer patients,[11,12] and others did not confirm the results.[13] The size of each individual study was not large enough to allow sufficient statistical power to assess any firm conclusion. A recently conducted meta-analysis[14] suffers all the limitations of all meta-analyses, such as the poor comparability of published data across studies and the inability to adjust the results for possible confounders. We conducted a pooled analysis of individual data of studies on CRP and overall survival; individual data allowed us to conduct a sensitivity analysis to find the optimal CRP cutoff predicting survival.

Materials and Methods

Original research studies that evaluated prostate cancer survival in relation to CRP levels were identified by searching the National Library of Medicine and National Institutes of Health PubMed database and Embase. The search strategy included the following keyword search terms: "prostate cancer," "outcome," "CRP," "C reactive protein," and spanned from January 1990 to January 2014. Reference lists from all retrieved articles were also reviewed in search of additional eligible articles.

Eligibility

Studies were considered eligible according to the following a priori criteria: (1) written in English; (2) availability of hazard ratio (HR) and 95% confidence interval (CI) data for CRP. Eight studies were identified; 2 of them were partially overlapping, and the most recent was used.[15,16] One study[13] reported the *P* value for the lack of association between survival and CRP, but did not include the HR. The total of eligible studies was therefore 6. Corresponding authors of identified studies were contacted and invited to share individual data to conduct a pooled analysis of the association between CRP and prostate cancer outcome. Two data sets were received (Table 1).[11,12,15,17-19]

Statistical Analysis

To evaluate the quality of the data, HR for mortality in relationship with CRP cutoff values was extracted from each study. Preliminary to the pooled analysis, meta-analysis computations were performed using the "metan" command in Stata (Stata Version 10, StataCorp LP, College Station, TX) was used. The combined HR was calculated according to a fixed and a random effects model; the Q statistics were used to test for heterogeneity between the studies included in the meta-analyses.[20] The I^2 statistic was used as a confirmatory test for heterogeneity,[21] with $I^2 < 25\%$, 25% to 50%, and $> 50\%$ representing low, moderate, and high degree of heterogeneity, respectively.

Pooled Analysis

Individual data from 2 data sets were received and analyzed for survival in relation to CRP. HRs and 95% CIs were calculated; multivariable Cox proportional hazards models provided estimates of overall survival, adjusted for age ($\leq$ and $>$ 71.9 years), and available prognostic factors: prostate-specific antigen ($\leq$ and $>$ 71.8 ng/mL), hemoglobin ($\leq$ and $>$ 12.5 g/dL), alkaline phosphatase ($\leq$ and $>$ 113 U/L). These cutoff points represented the median value for the analyzed population.

Analysis of the Optimal CRP Cutoff

The best cutoff of CRP was explored using X-title software version 3.6.1,[22] which is based on log-rank test statistics, where categorical (high/medium/low or high/low) CRP variables were

Table 1 Summary of Studies on the Association Between CRP and Prostate Cancer Survival

First Author	Country	n	Population	CRP Cutoff	HR for Survival	Estimate
Ito[17]	Japan	80	CRPC, at least 88% metastatic	≥5.0 mg/L	1.95 (1.33-2.96)	Crude
Nakashima[18]	Japan	126	Metastatic PC	≤15 mg/L	1.88 (1.03–3.45)	Adjusted
Beer[11]	US	160	mCRPC treated with docetaxel-based chemotherapy	8 mg/L	2.96 (1.52-5.77)	Adjusted
Pond[19,a]	US	116	mCRPC treated with docetaxel-based therapy; CRP prior to treatment	5.0 mg/L	1.68 (1.23-2.29)	Crude
Prins[12,a]	US	119	CRPC (90.8% mCRPC); various treatments, CRP prior to treatment			
McArdle[15]	UK	98	Localized PC	≤3; 3–10; >10	1.63 (1.08–2.45)	Crude
Total		699				
					Meta HR (95% CI)[b]	
Fixed Model					1.83 (1.51-2.21)	
Random Model					1.83 (1.51-2.21)	

Abbreviations: HR = hazard ratio; mCRPC = metastatic castration-resistant prostate cancer; PC = prostate cancer.
[a]Individual data received.
[b]Q statistics for heterogeneity: 2.7 ($P = .6$); I^2: < 5%.

generated, using the individual data from the available 2 data sets, and used as the predictor in Cox proportional hazards models. The best cutoff was defined as the point with the most significant split (ie, the maximum χ^2) among the survival distributions of those with different categorical CRP levels. The statistical significance was indicated with uncorrected and cross-validation *P* values. In addition, an adjusted *P* value based on the Miller-Siegmund method[23] was obtained for high/low models.

Results

There were 6 studies available, and 699 prostate cancer patients included. Two studies were conducted in Japan, 3 in the United States, 1 in the United Kingdom. Five studies included advanced prostate cancer, and one[15] included localized prostate cancer cases. The CRP cutoff value used in the original analysis varied from > 5 mg/L,[12,17,19] to 10 mg/L,[15] to 15 mg/L.[18]

All of the studies showed a statistically significant association between CRP and prostate cancer survival. The overall meta-HR (HR_{meta}) was 1.83 (95% CI, 1.51-2.21), without evidence of heterogeneity among studies (Q statistics: 2.7; $P = .6$; Figure 1). The analysis restricted to those studies that used a common cutoff point of 5 mg/L (3 studies[12,17,19]) produced an HR_{meta} of 1.78 (95% CI, 1.39-2.27), with no evidence of heterogeneity.

Pooled Analysis

There were individual data for 235 patients (2 of the 6 studies included in the meta-analysis[12,19]); their description is reported in Table 2. The crude HR_{pooled} for CRP < 5 versus ≥ 5 mg/L was 1.68 (95% CI, 1.23-2.29), the adjusted HR_{pooled} was 1.44 (95% CI, 1.02-20.4; Figure 1).

Optimal CRP Cutoff

Using the pooled analysis, the best CRP cutoff, when the option of 1 cutoff to compare high versus low levels was chosen, was 12 mg/L (corrected $P = .01$; uncorrected $P = .0005$). The HR_{pooled} for CRP < 12 versus ≥ 12 mg/L was 1.78 (95% CI, 1.29-2.47) and 1.53 (95% CI, 1.01-2.32) for the crude and adjusted models, respectively (Figure 2).

Figure 1 Pooled Estimates of Overall Survival of Prostate Cancer Patients According to C-Reactive Protein (CRP) Values (n = 235). * Adjusted for Age (≤ or > 71.9 Years), Prostate-Specific Antigen (≤ or > 71.8 ng/mL), Hemoglobin (≤ or > 12.5 g/dL), Alkaline Phosphatase (≤ or > 113 U/L) CRP ≤ 5 mg/L

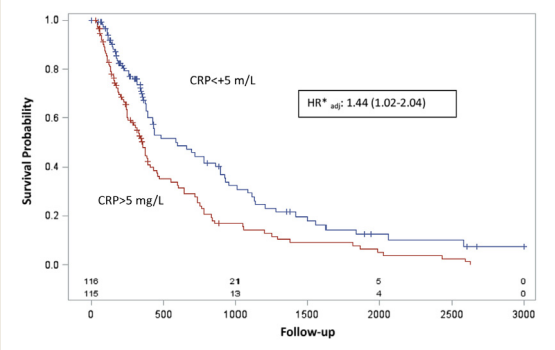


Table 2 Description of Patients Included in the Pooled Analysis (n = 235)

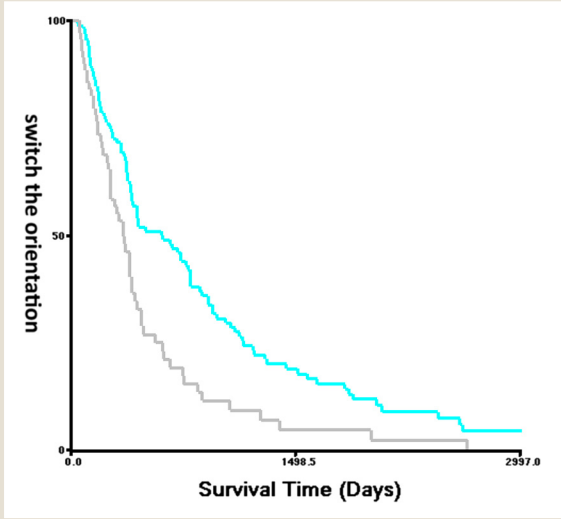
Variable	Mean ± SD (Range)	n (%)
Age, Years	71.3 ± 8.7 (45.8-91.5)	
CRP, mg/L	19.4 ± 39.1 (0.3-311)	
Hemoglobin, g/dL	12.4 ± 1.6 (7.4-16.7)	
Alkaline Phosphatase, U/L	194.3 ± 223.9 (33-1436)	
PSA, ng/mL	191.2 ± 327.3 (0.8-2112.6)	
Length of Follow-Up, Days	510 ± 578.6 (2-2997)	
Dead at Follow-Up		166 (70.6)
ECOG		
0		102 (43.4)
1		100 (42.6)
≥2		33 (14.0)

Abbreviations: CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen.

Discussion

The present pooled analysis confirmed previous findings of an association between CRP levels and overall survival. The meta-analysis of published studies suggests a statistically significant 83% increased risk of dying for patients with high CRP compared with those with low CRP levels. As always with meta-analyses, some limitations apply; the comparison across included studies show that the cutoff for CRP vary, with the most commonly used cutoff being 5 mg/L. A subset analysis was conducted on the studies relying on the same CRP cutoff, confirming the results of the larger analysis. Another limitation is the heterogeneity of the populations of prostate cancer patients included in each study. Some studies included

Figure 2 Survival Estimate Using the Best Cutoff Point of 12 mg/L



metastatic patients and others included localized prostate cancer patients. In addition, the summary estimates cannot be adjusted for possible confounders of the association, such as, for example other prognostic factors, or age.

In an attempt to overcome the limitations, a pooled analysis of individual data was conducted, including 235 patients. The pooled analysis indicated that a CRP value > 5 mg/L at baseline was a significant predictor of survival, even after adjusting the analyses for other prognostic factors. It should be noted that the patients in this pooled analysis were similar in that they had metastatic castration-resistant prostate cancer (mCRPC), many of whom received chemotherapy, but all were treated in an era before enzalutamide, abiraterone, cabazitaxel, sipuleucel-T, and radium-223, the 5 new therapies for mCRPC approved by the Food and Drug Administration since 2010.

This analysis has some weaknesses worth mentioning. Only 2 of the 6 data sets were available for the pooled analysis of individual data. Although the authors of the other publications were contacted several times and asked to send their data, they never responded. The data from the ASCENT (the **A**ndrogen-Independent Prostate Cancer **S**tudy of **C**alcitriol **EN**hancing **T**axotere) study were not available because the company that ran the study no longer exists. We were able to perform a more rudimentary analysis with all 6 studies using group, rather than individual adjusted statistics, and obtained similar results as the pooled analysis, specifically a statistically significant negative effect of increased CRP level on survival. However, the similarities and differences between the data submitted for the pooled analysis versus the data that was not submitted is worth mentioning. The 2 data sets received were homogeneous in that they were both from North America, and included men with mCRPC treated in a clinical trial. Two of the 4 data sets not submitted included patients treated in Japan,[17,18] 2 did not specify castration-resistant prostate cancer.[15,18] Even without the 4 other data sets, this is still the largest patient group to be analyzed for the prognostic value of CRP in prostate cancer. As always, there are limitations to this analysis: one is the lack of cancer-specific details. For example, Gleason grade values for half of the patients in the pooled analysis, and this prevented the inclusion of the Gleason score in the multivariate analysis. Gleason is an important factor in prognosis, but not every reported nomogram includes it. The Armstrong nomogram (TAX327-Docetaxel plus Prednisone or Mitoxantrone plus Prednisone) and Halabi nomogram (CLGB-B- radical prostatectomy alone versus estramustine and docetaxel before radical prostatectomy) used it, whereas the Armstrong risk groups, Smaletz nomogram and PCWG-2 (Prostate Cancer Working Group) clinical subtypes do not use it. Furthermore, we did not have access to full staging, for example, number of metastases, and this information could affect CRP values; full treatment details of the primary cancer (adjuvant radiation) was also incomplete. Other factors that could influence CRP values, for example, the presence of comorbidities, was not available in this sample of patients. Finally, the methods for CRP measurement in the article from Pond et al[19] were not known at the time of this analysis.

The biological reasons for the association between CRP and survival in prostate cancer are unclear. From the available data sets it is impossible to ascertain, for example, if CRP is increased because of the presence of cancer, or because of the immune state of the host, independent of other conditions or other chronic comorbidities such as infection or cardiovascular disease, because CRP is also an independent predictor of cardiovascular mortality.[24] It has been pointed out that CRP levels also increase as a response to chronic inflammation to ionizing radiation used for treating localized prostate cancer.[25] CRP also represents a regulating factor on tumor growth and proliferation,[26] thus it could contribute to cancer aggressiveness.

Another aspect to consider is that the association between CRP and cancer survival is not specific to prostate cancer, but has also been seen in other cancers.[9,27-30] It is possible that CRP simply reflects an enhanced immune response elicited by the tumor, and such response is more intense when local tissue damage and inflammation are high, as happens with more aggressive cancer subtypes. Interestingly, other markers of a systemic inflammatory and immune state have also appeared as prognostic in prostate cancer of different stages, and in other malignancies (eg, the neutrophil:lymphocyte ratio).[31]

Taking advantage of the data set available for analysis, we conducted a sensitivity analysis, to understand what the best CRP cutoff value is that could predict prostate cancer outcome. This analysis suggested that a value of 12 mg/L should be considered in future analyses.

The observation that a marker of inflammation, routinely measured as part of the baseline laboratory work in many clinical settings, could be used as a prognostic biomarker requires further investigation, including possibly interventions to modify CRP levels during cancer follow-up in an attempt to prevent recurrence and ultimately death. Another future path of research should be the study of local prostate tissue patterns among patients with high CRP levels, and the comparison with prostate tissues from patients with low CRP levels, in an attempt to understand if CRP reflects a specific aggressive microenvironment.

Conclusion

We report here the results of a pooled analysis showing a statistically significant association between increased CRP levels and survival. Because CRP is an affordable and readily available assay, it might hold promise in improving prognostication and potentially to predict the activity of specific therapeutic agents. Indeed, the prospective evaluation of CRP as a prognostic marker is ongoing in the AFFINITY (Cabazitaxel/Prednisone Alone or in Combination With Custirsen for 2nd Line Chemotherapy in Prostate Cancer) phase III trial, which is investigating the effect of combination treatment with custirsen and cabazitaxel in mCRPC. The test can be introduced in clinical routine evaluation only when prospective data will be available showing that CRP provides important information for prognosis.

Clinical Practice Points

- It has been suggested that high CRP levels are significantly associated with worse outcome in prostate cancer patients.
- A pooled analysis of 235 prostate cancer patients with complete clinical data showed that CRP is significantly associated with mortality.

- The best CRP cutoff to predict mortality was 12 mg/L.
- C-reactive protein, an easy and routinely performed laboratory test, could be considered in clinical practice to predict prostate cancer outcome and response to treatment.

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Disclosure

The authors have stated that they have no conflicts of interest.

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