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RESEARCH ARTICLE

C-Reactive Protein in Solid Tumors: Clinically Meaningful Change

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Abstract: Background: C-Reactive Protein (CRP) is associated with cancer development, survival, and tumor recurrence. A barrier to its use is the inability to interpret changes in CRP levels. **Aims**: The aim of this study was to determine when a change in CRP is clinically meaningful. **Methods**: This was a retrospective cohort study of consecutive cancer patients. Those with a solid tumor diagnosis and at least two consecutive CRP measurements post-diagnosis were included. Subjects were divided into Baseline High CRP (bHCRP; CRP $\geq$ 10 mg/L) and Baseline Normal CRP groups (bNCRP; CRP $<$ 10 mg/L), We identified appropriate CRP cut-off points for CRP levels changes; compared bHCRP and bNCRP; constructed Kaplan-Meier survival plots and Cox Proportional Hazard Model to confirm cut-off points in each group. **Results**: 1473 were eligible. In bHCRP group, Overall survival (OS) Mean (Standard Error) was 87(2) and 81(4) months for $\geq$ 50% *vs* $<$ 50% CRP decrease respectively. In bNCRP group, OS was 90(3) and 105(3) months for $\geq$ 2x *vs* $<$ 2x increase in CRP levels, respectively. These differences remained significant after adjusting for confounders. **Conclusion**: After a baseline normal CRP an increase of 2-fold or greater was associated with clinical and statistically significantly shorter OS. Conversely, after a baseline high CRP a 50% or greater decrease from baseline was associated with longer OS. Quantification of clinically meaningful CRP change could impact more effective CRP use as a biomarker, prognostic indicator and aid therapeutic decision making. This is especially important to reduce healthcare disparities in financially struggling healthcare systems.

Keywords: C-Reactive Protein, solid tumors, biomarker, overall survival

1 Introduction

C-Reactive Protein (CRP), part of the innate immune response, is produced mainly by the liver [1]. In healthy individuals, median CRP concentration is 0.8 mg/L (range 0-10 mg/L) [2]. The wide range is explained by genetic factors (50%) [3], age, body mass index, physical inactivity, race, and tobacco smoking [4, 5]. CRP levels $\geq$ 10 mg/L is associated with acute infection, autoimmune diseases, inflammation, trauma, and tumors [6]. Although Elevated CRP may persist in chronic conditions, it remains stable over time in healthy individuals making it a candidate for tumor screening [7, 8]. Indeed, elevated CRP in healthy subjects was associated with later cancer development [9–11]. This association was strongest in Asians (breast cancer), and in men (colorectal cancer) [12, 13]. We previously examined the relationship between a single CRP assessment and survival (N=4971); higher CRP values were associated with earlier death, even among those with higher normal levels [14]. Also, tumor expressed CRP when present, was independently associated with survival [15].

In cancer, high CRP was prognostic in 90% of 271 studies and associated with recurrence [16]. Hybrid scores with albumin were created: CRP/Albumin Ratio, Glasgow Prognostic Score (GPS), and modified GPS [17]. Despite the association between CRP and later cancer development, shorter survival, and cancer recurrence, it is used inconsistently in routine practice. A major challenge is the inability to interpret changes in CRP levels. The objective of this study was to determine when a change in CRP is clinically meaningful.

2 Material and Methods

2.1 Study Design/Population/Measures

This is a rretrospective cohort study of electronic medical records (EMR; My Practice/EPIC, Epic Systems Corporation, WI, USA). The Cleveland Clinic IRB approved the protocol and

waived informed consent. Consecutive subjects presenting, to the Taussig Cancer Institute, between 2006-2012 with a solid tumor, and at least two CRP measurements post-diagnosis were included. We excluded age < 18, CRP assessments < 7 days apart, hematologic malignancy, or those with missing data. We used the first CRP value present after diagnosis (baseline) and the second value reported thereafter. In 2020, we retrieved death date from the EMR or Social Security Death Index. The endpoint was overall survival (OS), defined as months from tumor diagnosis to death. Detailed description of data elements was reported elsewhere [16]. Subjects were divided into baseline: high CRP (bHCRP; CRP $\geq$ 10 mg/L) and normal CRP groups (bNCRP; CRP $<$ 10 mg/L) because these groups were biologically different (Table 1).

Table 1 Patients' Demographic and Baseline Characteristics

Variable	Sub-Variable	Baseline High C-Reactive Protein (N = 943)		Baseline Normal C-reactive Protein (N = 530)		P-Value
		N	%	N	%	
Gender	Female	484	51%	323	61%	< 0.05
	Male	459	49%	207	39%	
Race	African American	128	14%	74	14%	NS
	Caucasian	776	82%	442	83%	
	Other	39	4%	14	3%	
Diagnosis	Breast	147	16%	115	22%	< 0.05
	Gastrointestinal	152	16%	45	8%	
	Multiple	131	14%	55	10%	
	Others	312	33%	182	34%	
	Prostate	112	12%	60	11%	
	Skin	89	9%	73	14%	
MetastaticDisease	Yes	259	27%	91	17%	< 0.0001
Comorbidities	Heart	173	18%	83	16%	NS
	Inflammatory Bowel Disease	29	3%	21	4%	NS
	Joint Disease	130	14%	94	18%	0.04
	Liver	102	11%	21	4%	< 0.0001
	Venous Thrombo-Embolic Disease	192	20%	93	18%	NS
	Total	447	47%	253	48%	NS
Therapies	Aspirin	270	29%	144	27%	NS
	Chemotherapy	218	23%	151	28%	< 0.05
	Corticosteroids	284	30%	167	32%	NS
	Hormone	83	9%	57	11%	NS
	NSAIDS[a]	172	18%	115	22%	NS
	Statins	299	32%	184	35%	NS
	Surgery	258	27%	62	12%	< 0.05
Dead		360	38%	136	26%	< 0.05
C-Reactive Protein Categories	Total	943	100%	530	100%	< 0.0001
	Decrease	555	59%	111	21%	
	Increase	280	30%	347	65%	
	Stable	108	11 %	72	14%	
Age(years)	Mean (SD) At Diagnosis	Median (R) 64 (13)	Mean (SD) 65 (18-91)	Median (R) 65 (13)	66 (18-94)	NS
C-Reactive Protein (mg/dl)		72 (76)	41(10-490)	5 (2)	5 (1-10)	< 0.0001
Total White Blood Cell Count(10^9/L)		9 (4)	8 (1-32)	8 (3)	7 (0-38)	< 0.0001
Body Mass Index(kg/m2)		28 (7)	27(10-65)	28 (7)	28 (14-69)	< 0.05
Survival (months)		53 (29)	50 (1-137)	62 (31)	61 (2-134)	< 0.0001

Note: [a] Other than Aspirin; p-value < 0.05 is considered statistically significant.

2.2 Statistical Analysis

We report mean and standard deviation/error (SD/SE) or median and range (R) for continuous variables; and counts and percentages (%) for categorical variables. Percentages were rounded to the nearest whole number and numbers to one significant figure, unless otherwise specified. Categorical variables were compared by the Chi-square test or Fisher Exact test, and continuous variables by appropriate parametric and nonparametric tests.

Percentage change in CRP (%ΔCRP) was defined as ((second CRP assessment– baseline CRP

assessment) /baseline CRP assessment)) × 100. Cut-off points for %ΔCRP was determined using literature reports, median and quartile range, and/or Receiver Operator Curve analysis, when an appropriate sample size was available [18]. We determined the Cut-off points to be 50% decrease or a 2-fold increase in CRP. To confirm cut off points we used Kaplan-Meier survival plots, log-rank test, and constructed Cox Proportional Hazard Model (CPHM) for bHCRP and bNCRP groups separately. Models were adjusted to account for potential confounders (Age; Body Mass Index; Cancer Site and Stage; Cancer Treatment; Comorbidities: arthritis, gastro-intestinal, heart, inflammatory, liver, and thromboembolic diseases; Gender; Metastatic Disease; Race; White Blood Cell Count (proxy for inflammation and infection)). Results are shown as hazard ratios (HR) with 95% confidence intervals (CI). We used Goodness-of-Fit to assess CPHM. Variables significant on univariate analysis or of known clinical significance were included in the models. A clinically meaningful survival benefit was reported to be two months or more [19]. Sample size calculation was not done due to the exploratory nature of this study. Statistical tests were two-sided and a p-value < 0.05 indicated statistical significance. Analyses were performed with SAS software (SAS® OnDemand for Academics. Cary, NC: SAS Institute Inc.).

3 Results

Demographic: 7716 presented with a solid tumor (2006–2012). 1473 had at least two CRP assessments $\geq$ 7 days apart. Those in the bNCRP group (n = 530) were more likely to be female, breast or skin cancer, lower BMI, and longer OS. The bHCRP group (n = 943) was more likely gastrointestinal cancers, higher total white blood cell count, liver disease, metastatic disease, and prior surgery (Table 1).

Kaplan Meier Survival Estimation: OS in bHCRP was, mean(SE), 87(2) and 81(4) months for subsequent $\geq$ 50% and $<$ 50% CRP decrease; and in bNCRP, 90(3) and 105(3) months for $\geq$ 2-fold and $<$ 2-fold increase (Figure 1 and 2).

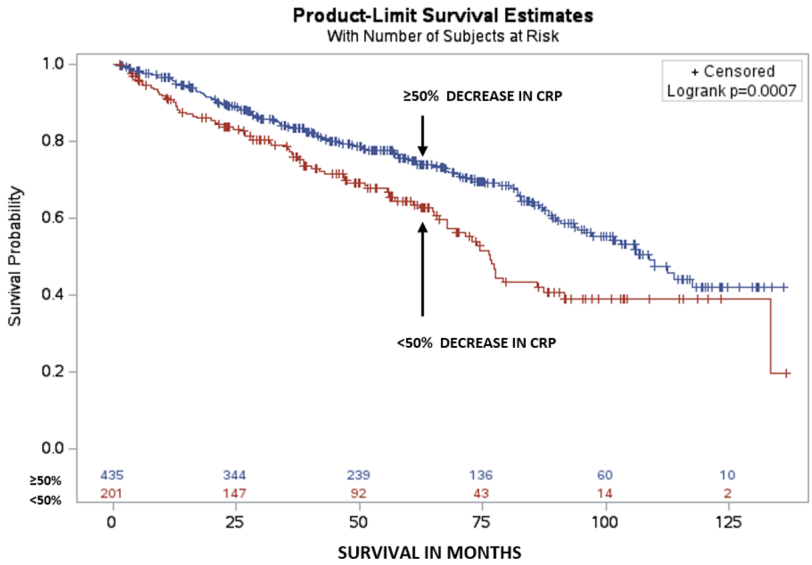

Figure 1 Kaplan Meier Survival Curves: CRP Decrease ($\geq$ 50% *vs* $<$ 50%) Following an Initial High CRP, and Overall Survival.

Cox Proportional Model Analysis: In bHCRP, CRP increase did not predict OS, but a $\geq$ 50% decrease had a 40% lower mortality risk compared to $<$ 50%. In bNCRP, a CRP decrease did not predict OS, but a $\geq$ 2-fold increase doubled the mortality risk compared to a lower increase (Table 2).

4 Discussion

We were able to quantify "how much change in CRP is significant" after cancer diagnosis. At least a 2-fold increase after a bNCRP and a 50% decrease in bHCRP was associated with OS. That remained statistically and clinically meaningful after adjustment for confounders.

No prior studies, to our knowledge, examined longitudinal CRP changes post cancer diagnosis.

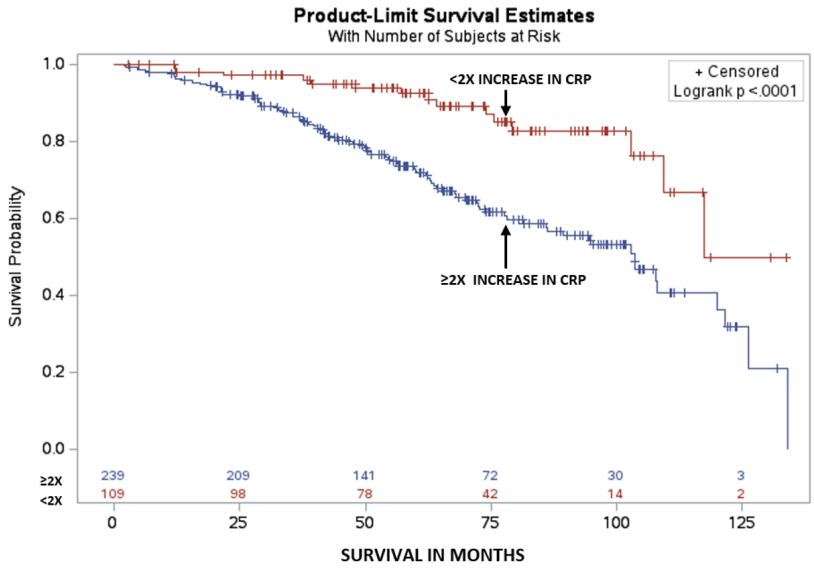

Figure 2 Kaplan Meier Survival Curves: CRP increase ($\geq$ 2-Fold Versus $<$ 2-Fold) Following an Initial Normal CRP, and Overall Survival.

Table 2 COX Proportional Hazard Models for Overall Survival in Baseline High C-Reactive Protein Group and Baseline Normal CRP Group

Parameter		DF	Estimate	SE	Chi-Square	P-Value	HR	% Confidence Limits	
Baseline High Crp CRP Change (Reference Increase $<$ 2x)	Decrease $\geq$ 50% Decrease $<$ 50% Increase $\geq$ 2X	1	-0.4	0.2	6.7	$<$ 0.01 ns ns	0.6	0.5	0.9
Baseline Normal Crp CRP Change (Reference Decrease $<$ 50%)	Increase $\geq$ 2x Increase $<$ 2x Decrease $\geq$ 50%	1	0.7	0.3	5.4	$<$ 0.05 ns ns	2.1	1.1	2.6

Note: DF: Degrees of Freedom; HR: Hazard Ratio; p-value $<$ 0.05 is considered statistically significant. Model adjusted for Age; Body Mass Index; Cancer Site and Stage; Cancer Treatment: Chemotherapy, Surgery; Comorbidities: arthritis, gastro-intestinal, heart, inflammatory, liver, and thromboembolic diseases; Gender; Metastatic Disease; Race; White Blood Cell Count (proxy for infection)

Two studies evaluated the risk of de novo cancer development. In a Danish general population (N=10,408; follow up for16 years) the risk of new cancer development was 2-fold for lung cancer in the highest versus lowest CRP quintiles [9]. Similarly in another study (N=592), there was a 2-fold greater risk of de novo cancer development [10]. Although these studies lacked post diagnosis longitudinal CRP assessment, they lend support to use of a 2-fold CRP increase as clinically important.

Limitations: unknown indication for CRP assessment; although we accounted for multiple conditions an unknown confounder may still bias the results, dividing subjects reduced final subgroups' sample sizes. Future studies should conduct a more comprehensive evaluation in a larger prospective design to confirm our findings and confirm their generalizability.

CRP is a cheap, readily available, non-invasive biomarker. It could be used in multiple solid tumors using our approach to screen for disease progression or regression. We present a novel approach to interpret CRP changes, in a large sample, of mixed solid tumors, representative of those typically presenting to a cancer center. We did not incorporate complex CRP and albumin algorithms in favor of a simple method easily incorporated into practice. We defined parameters for clinically meaningful change in CRP in cancer patients. This will reduce healthcare disparities in cash-strapped systems.

5 Conclusions

In solid tumors, after a baseline normal CRP an increase of at least 2-fold reflects shorter OS, while a decrease of at least 50% after a baseline high CRP, was associated with longer OS. Serial CRP measurement after diagnosis may accurately reflect disease progression or regression. Quantification of clinically meaningful CRP change could eliminate a barrier to more effective CRP use as a biomarker and prognostic indicator and aid therapeutic decision making. Use of a

cheap biomarkers like CRP will reduce health disparities especially in developing countries. A large prospective study is needed to confirm our findings.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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