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ORIGINAL ARTICLE

CRP evaluation in non-small cell lung cancer

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Abstract *Background:* CRP is an inflammatory mediator that is shown to be elevated in different inflammatory and malignant conditions, the aim of the study to see whether the elevated serum CRP is correlated with the advanced stages and increased tumor size of NSCLC after exclusion of patients with high CRP due to infection.

Materials and methods: 71 patients with proved NSCLC and 25 healthy control volunteers were selected for the study, serum CRP and PCT were analyzed, results of CRP in patients with NSCLC were compared with the control group, and subgroups were made according to different clinical variables as subtypes of lung cancer, tumor staging and tumor size.

Results: The serum CRP level was significantly higher in patients with NSCLC compared to the control group 114.2 ± 60.1 mg/ml vs. 13.4 ± 8.6 mg/ml) with *p* value < 0.001, no significant difference was recorded in PCT level ($p > 0.05$), there was no significant difference between NSCLC subtypes ($p > 0.05$), there was a positive correlation between CRP level and tumor size ($p < 0.01$), TNM tumor staging ($p < 0.01$).

Conclusion: CRP is an inflammatory biomarker that is shown to be elevated in NSCLC and its elevation is correlated with the tumor size and tumor staging but not to subtypes of NSCLC, it may point to poor outcome and poorer prognosis.

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Introduction

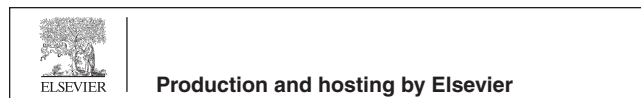C-reactive protein (CRP) was discovered in 1930 and is widely used as a sensitive, but nonspecific, marker of systemic inflammation [1]. C-reactive protein (CRP) is the prototype acute-phase protein, which can increase up to 1000-fold after the onset of a stimulus. Aside from its disputed role as a marker of infection and/or inflammation in daily clinical practice, the protein has a wide variety of biological properties and functions [2]. Increased serum CRP (s-CRP) levels have been reported in many pulmonary disorders, including pneumonia, malignancies, and pulmonary thromboembolism [3].

The elevated levels of CRP are associated with an increased risk of all-cancer, lung cancer, and possibly breast, prostate and colorectal cancer [4]. And it is positively correlated with weight loss, anorexia-cachexia syndrome, extent of disease, and recurrence in advanced cancer [5].

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The reasons for CRP elevation in cancer patients are not clearly understood, several possible mechanisms have been proposed for the relationship between CRP and cancer [6]. Some stated that tumor cells themselves cause tissue inflammation and thus increase CRP levels, and the presence of Malignant Pleural Effusion usually indicates the severity of illness and a short survival time [7].

One possible explanation is that, due to cytokine production by tumor tissue, elevated CRP values may indicate a higher tumor burden [6]. Of the cytokines that has been implicated as the cause of increased CRP production is IL-6 [8]. The catabolic effect of acute-phase proteins like CRP on metabolism, and this is associated with an increase in resting energy expenditure and loss of lean tissue in patients with lung cancer [9]. Another reason for elevated CRP may be a cancer-related infection, particularly a post-stenotic pulmonary infection in the case of lung tumors. It is well known that pneumonia may be the first sign that marks lung cancer [10]. In cases of lung cancer CRP may be falsely elevated as a result of infections that are encountered during the course of disease and increase the incidence of morbidity and mortality [11].

In patients with non-small cell lung cancer (NSCLC), elevated CRP levels prior to therapy have been shown to have an adverse impact on prognosis [12].

Procalcitonin (PCT), a precursor of the hormone calcitonin, participates in the systemic reaction in response to the circulating endotoxins and inflammatory cytokines produced during bacterial or fungal infections. Its plasma levels are correlated with the severity of infection [13]. Procalcitonin has been shown to be important in the differential diagnosis of cancer patients with fever and high CRP levels [14].

The aim of our study is to correlate the level of CRP to TNM classification of NSCLC cases and also tumor size after exclusion of cases with high CRP due to bacterial infection or sepsis detected by analyzing the serum procalcitonin level.

Subjects and methods

Patients who were newly diagnosed with NSCLC lung cancer in the period from July 2010 to January 2013 were included in this prospective study (71 patients) and 25 of apparently healthy volunteers were set as a control group, exclusion criteria were patients diagnosed with small cell lung cancer, patients under chemotherapy, radiation therapy or any history of either, use of anti-inflammatory drugs or systemic steroids, presence of inflammatory disease or sepsis that could alter the results of CRP by detecting a high procalcitonin (PCT) level (above 0.5 ng/ml), patients with high PCT may be re-enrolled after treatment of their infection or inflammation. All of the recruited patients and volunteers provided written informed consent.

All patients and control group were evaluated by thorough history taking including age, sex, body mass index (BMI) and concomitant diseases of the patients were recorded, complete physical examination followed by chest X-ray and chest CT scans where radiological assessment of lung *cancer staging* was done using TNM classification and also the *maximum cancer diameter* was assessed and calculated, pulmonary function testing together with routine laboratory testing. In the patient group diagnosis was made either by bronchoscopic biopsies in accessible lesions, transthoracic needle biopsy in peripheral lesions, pleural fluid aspiration in cases of concomitant malignant pleural effusion, excisional lung biopsies in cases not accessible by bronchoscopy or transthoracic route, transbronchial needle aspiration from subcarinal lymph nodes was done for the diagnosis and staging if subcarinal LN size is larger than 1 cm, all patients were subjected to MRI brain abdominal CT scan and bone scintigraphy for an accurate assessment of distant metastases, after full investigation the TNM classification of each patient was recorded and serum CRP was analyzed together with serum procalcitonin.

Peripheral venous blood was obtained under sterile conditions both in patients with a confirmed histological diagnosis of NSCLC and the healthy controls. Serum was separated by centrifuging for 10 min at $1000g$ and 4 °C in vacuum gel tubes, and then kept at –80 °C in Eppendorf tubes until the time of assay. All samples were assayed on the same day. CRP was analyzed by routine clinical laboratory test protocols using an automated chemical analyzer (Modular P800; Roche Diagnostics GmbH, Mannheim, Germany).

The serum level of PCT was measured by using an enzyme linked fluorescence assay (VIDAS® BRAHMS PCT assay; Biomérieux, Lyon, France) according to the manufacturer's instructions and serum CRP levels were assayed by nephelometry using an automated system (Dade Behring).

Statistical analysis

Data were statistically described in terms of mean (standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. Comparison of numerical variables between more than two groups was done using Kruskal Wallis test. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value of CRP in diagnosing malignancy. p values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

71 patients with diagnosed NSCLC (8 females and 63 males) and 25 control cases (5 females and 20 males) were subjected to the study, there is no statistical significance between the control group and the study patients in the age, gender, smoking habits and BMI as seen in Table 1, 56 patients (78.87%) patients were diagnosed by bronchoscopic biopsies, 11 patients (15.49%) by either thoracoscopy or mediastinoscopy and 4 patients (5.63%) by open thoracotomy. Different histopathological subtypes of NSCLC were categorized as squamous cell carcinoma 31 (43.6%), adenocarcinoma 25 (35.2%) alveolar cell carcinoma 9 (12.6%) and the other groups of NSCLC including undifferentiated subtypes and unclassified cases 6 (8.4%).

Table 1 Patient and control clinical characteristics.

		Patients	Control	*p* Value
Age (year) mean ± SD		60.2 ± 7.8	56 ± 8.8	> 0.05
Gender	Males *n* (%)	63 (88.7%)	20 (80%)	> 0.05
	Females *n* (%)	8 (11.3%)	5 (20%)	> 0.05
Smoking habit	Current smokers *n* (%)	45 (63.4%)	12 (48%)	> 0.05
	Ex-smokers *n* (%)	12 (16.9%)	3 (12%)	> 0.05
	Non-smokers *n* (%)	14 (19.7%)	10 (40%)	> 0.05
BMI mean ± SD		26.6 ± 2.5	27.2 ± 2.0	> 0.05
Method of diagnosis	Bronchoscopy *n* (%)	56 (78.87%)		
	Thoracoscopy or mediastinoscopy *n* (%)	11 (15.49%)		
	Thoracotomy *n* (%)	4 (5.63%)		
Serum CRP (mg/dl) mean ± SD	114.2 ± 60.1		13.4 ± 8.6	< 0.001
Serum PCT (ng/ml) mean ± SD	0.22 ± 0.15		0.23 ± 0.16	> 0.05

There was no significance between the patient group and the control group as regards PCT level 0.22 ± 0.15 ng/ml vs. 0.23 ± 0.16 ng/ml *p* value > 0.05 Fig. 1 indicating the absence of bacterial infection in both groups. Also No significant differences were evidenced when comparing the PCT concentration values of NSCLC patients according to different patient characteristics and tumor stages. All PCT levels in the patient group as well as the control group were below the cutoff point for the test which is 0.5 ng/ml.

The serum CRP was statistically higher in the patient group compared to the control group (114.2 ± 60.1 mg/ml vs. 13.4 ± 8.6 mg/ml) with *p* value < 0.001 Fig. 2. The serum CRP level was studied according to patients with different histo-pathological subtypes of NSCLC, the stage of the disease and tumor size, data are summarized in Table 2, mean serum CRP values for subtypes were 159.87 ± 58.45 mg/dl for squamous cell carcinoma, 137.88 ± 61.2 mg/ml for adenocarcinoma 155.00 ± 74.869 mg/ml for alveolar cell carcinoma and 127.83 ± 54.92 mg/ml for group entitled under others with *p* value more than 0.05 as shown in Fig. 3.

Different subtypes of NSCLC were compared as regards serum CRP and the results did not show statistical significance shown in Table 2 and Fig. 3.

The size of the primary lesion in the patient group was analyzed and the correlation between the size and the level of serum CRP showed a positive linear relationship with a *r* < 0.5 and a *p* value > 0.05 as shown in Fig 4.
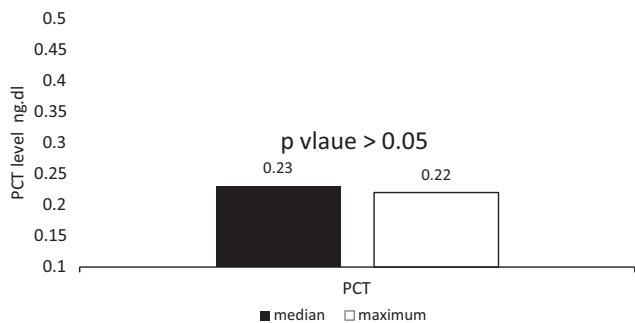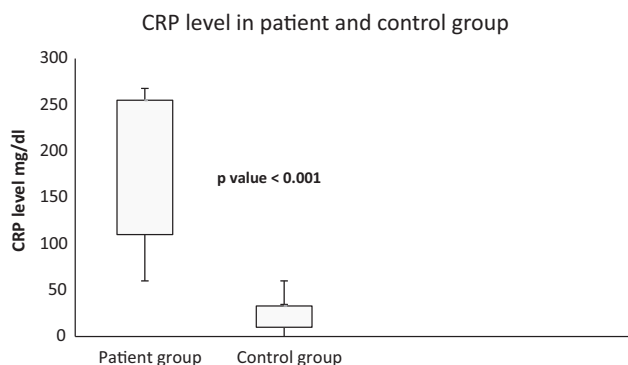

Figure 2 Box plots showing CRP levels in patients with non-small cell lung cancer and control group 110 (17–155) mg/dl and 10 (3–33) mg/dl; *p* < 0.001.

In the patient group the tumors were further classified according to the TNM classification into stage 1A, 1B, 2A, 2B, 3A, 3B, and 4, none of the tumors was found in stage 1A, 2 (2.8%) stage 1B, 8.5% stage 2A, 15.5% stage 2B, 19.7% stage 3A, 38% stage 3B, and 15.5% stage 4, the comparison of mean maximum and minimum CRP among different stages of NSCLC did not reach a statistically significant value (Figs. 5 and 6).

Discussion

In this study the main finding is the presence of a significant increase of the CRP level among patients with NSCLC compared to control subjects and there was no significant difference in the serum procalcitonin level indicating that the rise of CRP in the patient group was not related to infectious etiology. Serum procalcitonin is seen higher in patients with active bacterial infection and there is no available data in the literature to support rise of PCT in various cancer patients so it was used to exclude patients with lung cancer associated with infectious etiology. Procalcitonin as a more sensitive test than CRP for bacterial infections was reviewed in different studies [15].

Serum CRP levels, measurement of which is relatively inexpensive and easy to quantify in daily clinical practice and it is used in various studies to diagnose, evaluate the prognosis or response to treatment. In general, patients with cancer have


Figure 1 Median procalcitonin (PCT) level in the patient and control groups with no statistically significant difference (*p* value > 0.05).

Table 2 Serum CRP levels (mg/dl) for different subtypes of NSCLC, tumor stage according to TNM classification, and tumor size (size less than or equal to 7 cm was taken as cutoff as mean size).

		n (%)	CRP mean ± SD (mg/ml)	p Value
Tumor type	Squamous cell carcinoma	31 (43.6%)	159.87 ± 58.45	> 0.05
	Adenocarcinoma	25 (35.2%)	137.88 ± 61.2	
	Alveolar cell carcinoma	9 (12.6)	155.00 ± 74.86	
	Others	6 (8.4%)	127.83 ± 54.92	
Tumor stage (TNM)	1B	2 (2.8%)	53.52 ± 13.3	< 0.001
	2A	6 (8.5%)	44.85 ± 16.61	
	2B	11 (15.5%)	65.53 ± 38.57	
	3A	14 (19.7%)	110.33 ± 53.37	
	3B	27 (38%)	155.85 ± 65.71	
	4	11(15.5%)	170.05 ± 60.50	
Tumor size	Size ⩽ 7 cm	52 (73.2%)	110.27 ± 69.55	< 0.001
	Size > 7 cm	19 (26.7%)	167.38 ± 53.80	
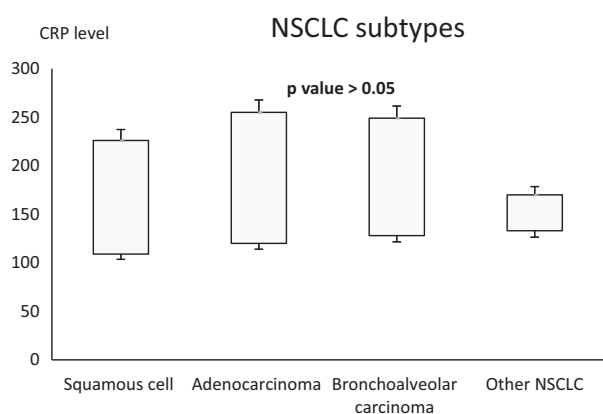
Figure 3 CRP level in different subtypes of non-small cell lung cancer (NSCLC) showing non-statistical significant difference ($p > 0.05$).
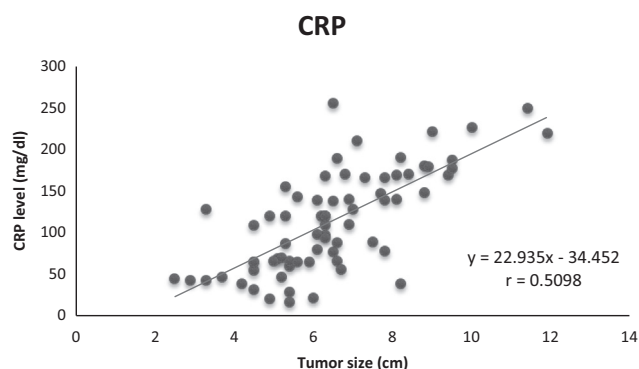
Figure 4 Scatter diagram for the correlation coefficient between tumor size (horizontal axis) and serum CRP level (vertical axis) showing a significant linear relationship ($r = 0.509$, $p < 0.05$).

been shown to have higher CRP concentrations than healthy controls and participants with some benign diseases [16].

The elevated serum CRP is strongly related to risk of cancers especially lung cancer in a recent meta-analysis study by Yong-Guo et al. [17], and it was not known whether the
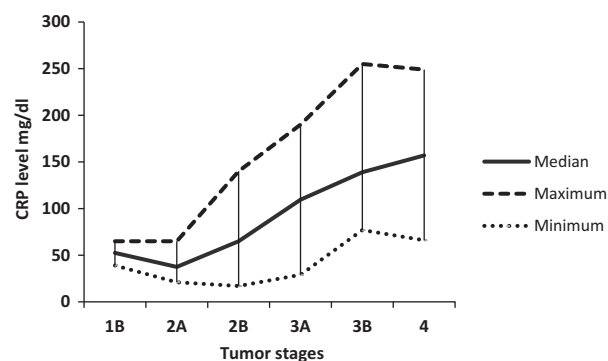
Figure 5 Serum CRP levels in patient group as classified according to TNM (with median maximum and minimum values).

elevation of CRP represents a carcinogenic effect participation or that the elevated CRP is a tumor marker itself.

Several possible mechanisms have been proposed for the relationship between CRP and cancer. First, tumor growth can cause tissue inflammation and hence increase CRP levels [18,19]. Second, CRP could be an indicator of an immune response to tumor antigens [20–22]. Third, there is evidence that cancer cells can increase the production of inflammatory proteins, which could explain the high CRP concentrations in patients with cancer. Some cancerous cells have been shown to express CRP [23–25]. And cancer cell lines have been shown to secrete IL6 and IL8, which in turn induce the production of CRP [26,27]. These mechanisms imply that increased CRP is a response to the neoplastic process and that CRP concentrations could thus provide a marker for identifying people with cancer at an early stage when treatment might be more effective. Finally, chronic inflammation, of which CRP is an important marker, might have an etiological role in cancer. This last factor has not been included in the present study by performing serum procalcitonin level to all patients and excluding them if the test is positive.

In this study we found there is a positive correlation coefficient between serum CRP level and pathologic tumor diameter, we selected 7 cm as a mean tumor diameter in our study and the serum CRP level for tumors with a diameter higher than 7 cm was statistically higher (167.38 ± 53.80 vs.
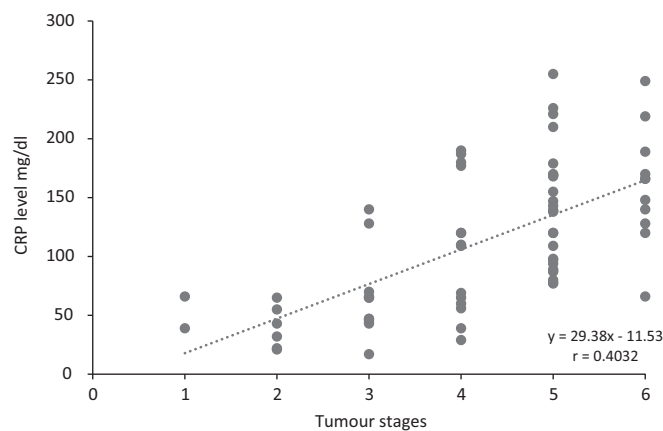
Figure 6 Levels of CRP in different stages of NSCLC according to TNM classification, 1 = stage1B, 2 = stage 2A, 3 = stage 2B, 4 = stage 3A, 5 = stage 3B, 6 = stage 4 (r = 0.403 and p value < 0.05).

110.27 ± 69.55 p value < 0.001), this is matching with a study done by Lee et al. [28] in surgically resected specimens showing increased CRP level with lymphovascular spread and pathologic tumor size, on the contrary Lee et al. found a higher serum level with squamous cell carcinoma versus non-squamous cancer which we could not prove in the present study. Tulek et al. also did not find a correlation between tumor pathological subtype and CRP level.

In this study we found a positive correlation between the CRP level and the tumor stage (p value < 0.001), a finding which was present in a study that demonstrated a relationship between tumor diameter and higher level of CRP but weakly [29].

Most of the studies attempting to evaluate the use of circulating CRP in the diagnosis of various cancers did not present relevant statistical analyses and most of the vast literature published on the association of circulating CRP with cancer are based on studies of prevalent cancer cases [6], which cannot provide evidence for causality but different studies support the poor prognosis when patients with NSCLC [30] or small cell lung cancer [31] show a high serum CRP level. As shown in the present study there was a statistically significant higher level of CRP associated with advanced stages of NSCLC and also with larger tumor size, indicating poorer prognosis.

The elevation of CRP is not known to be either related to the tumor itself or increased with size and stage as shown in this study or it is related to the nature of the patient who develops NSCLC as some studies [4] showed elevated CRP as a risk factor for carcinogenesis, which support a role of chronic inflammation in carcinogenesis. But based on current knowledge, baseline CRP measurement is not recommended for the prediction of cancer incidence and cancer screening. Further studies are needed to identify whether CRP, as a marker of inflammation, has a direct role in carcinogenesis. But the response to chemotherapy was shown to be inferior in patients with higher pretreatment levels of CRP indicating poorer prognosis [32], and the same was seen in surgical resection of NSCLC cases with high pre-operative CRP compared to low CRP [33].

The weak points in this study are the small number of patients and the study is done on already diagnosed cases which do not reflect the actual clinical practice, but it can be used as a tool to predict the prognosis toward chemotherapy or operability.

In conclusion, CRP is an inflammatory biomarker that is shown to be elevated in NSCLC and its elevation is correlated with the tumor size and tumor staging but not to subtypes of NSCLC, it may point to poor outcome and poorer prognosis.

Conflict of interest

None.

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