

Association of Serum CRP level with Lung Cancer and Healthy Control of North Indian Population

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ABSTRACT- Background- Lung cancer is the major cause of cancer-related mortality worldwide. Chronic inflammation of the airway plays an important role in the alternations of bronchial epithelium and lung microenvironment, therefore provoking the pulmonary carcinogenesis and progression of lung cancer. The results may suggest that high inflammation level can be associated with the higher risk of lung cancer. CRP is an acute-phase protein produced in the liver in response to elevated cytokine levels after an inflammatory stimulus. C-reactive protein (CRP) a systemic marker of chronic inflammation is associated with increased lung cancer risk.

Methods- This case-control study was conducted on 40 lung cancer patients and 30 healthy controls. CRP level was measured in serum by ELISA kits.

Results- Elevated serum CRP level was found in lung cancer patients as comparison to healthy controls. This study shows significant association between the serum CRP level of lung cancer patients and healthy controls ($p < 0.0001$) and also showed significant association between smoker, ex-smoker and non-smokers lung cancer patients as well as in healthy controls ($p < 0.0001$).

Conclusions- Higher CRP levels were found in lung cancer patients as compared to healthy controls. The higher CRP level was also observed in Smoker, Ex-smoker as compared to a non-smoker in lung cancer patients and healthy control.

Key-words- Biomarker, Lung Cancer, CRP, Cardiovascular disease, Inflammatory Stimulus

INTRODUCTION

Lung cancer is the major cause of cancer-related mortality in both men and women worldwide^[1]. Chronic inflammation in airway plays an important role in the alternations of bronchial epithelium and lung microenvironment provoking the pulmonary carcinogenesis and progression of lung cancer. The results may suggest that high inflammation level can be associated with the higher risk of lung cancer. It is known that pro-inflammatory cytokines such as interleukin 1, interleukin 2, tumor necrosis factor alpha and tumor growth factor are able to stimulate the production of C-reactive protein (CRP) as well as influence survival, growth, mutation, proliferation, differentiation, and migration of tumor cells^[2]. C-reactive protein (CRP) a

systemic marker of chronic inflammation increases during the host response to tissue injuries such as infection, trauma, myocardial infarction and surgery^[3]. Serum CRP levels are associated with the risk of cardiovascular disease, colon cancer and elevated levels of CRP have been reported as a risk factor for the development of colon cancer also^[4,5]. CRP is an acute-phase protein produced in the liver in response to elevated cytokine levels after an inflammatory stimulus^[6]. It has been found that acute-phase response is also seen in a variety of diseases such as cardiovascular disease, diabetes, systemic inflammatory diseases, some autoimmune disorders and cancer^[7,8]. CRP levels have also been used to predict cancer risk, detect cancer recurrence and determine prognosis^[9-11]. Elevated preoperative serum CRP has been identified to be a significant prognostic factor in patients with colorectal, oesophageal and hepatic carcinoma. Several studies have shown that NSCLC Patients with elevated preoperative serum CRP levels has worse survival than those patients with undetectable levels of CRP^[12-14]. It is well known that chronic inflammation is associated with lung carcinogenesis. C-reactive protein (CRP) a systemic

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marker of chronic inflammation is associated with increased lung cancer risk. Elevated levels of C-reactive protein (CRP) have been associated with increased lung cancer risk in several retrospectives and a few prospective studies [15-19]. It can serve as a good biomarker as measuring levels at baseline will be helpful in assessing severity and determining the progression of diseases like COPD and lung cancer. Measuring CRP levels will also be helpful in determining the efficacy of treatment [20,21]. This study aims to determine the serum CRP level in lung cancer and healthy control and its association with the smoking status.

MATERIALS AND METHODS

This study was conducted at the Department of Respiratory Medicine, King George's Medical University, Lucknow, India. This study was approved by the ethics committee of the corresponding institution and participants gave their written informed consent. A total of 40 histopathologically confirmed lung cancer patients were enrolled in this study after excluding those having other disorders such as COPD, asthma, tuberculosis, interstitial lung disease, and 30 healthy controls without having the past history of any chronic or acute disease for last one month were also enrolled to compare the serum CRP levels of both the groups. Peripheral blood samples of lung cancer patients and controls were collected. The blood sample was centrifuged for the separation of serum, stored at -80°C until analysis. Serum CRP level of lung cancer patients and healthy controls were determined by the ELISA method according to manufacture's instruction.

Statistical Analysis- Data were analyzed using Graph Pad Prism version 5 (Graph Pad Software Inc.; La, Jolla, CA, USA). All demographic and clinical data were expressed as mean \pm standard error of the mean (SEM) and percentage. The chi-square test was used for categorical data and groups were compared by unpaired t-test or one-way analysis of variance (ANOVA), $p < 0.05$ was considered significant.

RESULTS

The demographic and clinical characteristics of lung cancer patients and controls are shown in Table 1. The mean age of the lung cancer patients and control group were not showing significant different ($p=0.45$). Out of 40 lung cancer patients 33(82.5%) was male and 7(17.5%) were female. The study also comprises 24(80%) healthy control male and 6(20%) healthy control female. This study comprises 19(47.5%) smokers, 8(20%) Ex-smoker and 13(32.5%) Non-smoker Lung cancer while 9(30%) smoker, 5(16.7%) ex-smoker and 16(53.3%) non-smoker control. A non-significant difference was found in the smoking history of lung cancer patients and control ($p=0.215$). It has been observed that the weight and BMI were lower in the lung cancer patients as compared to controls and this difference is statistically significant ($p < 0.0001$). In the

present study 19(47.5%) lung cancer patients were of adenocarcinoma and 17(42.5%) were squamous cell carcinoma. Majority of lung cancer patients 37(92.2%) were stage iii/iv. Serum CRP level was elevated in lung cancer patients as compared to control (Fig. 1). In this study, the significant association was observed in the serum CRP level ($P < 0.0001$) in lung cancer patient and healthy control. Levels of serum CRP between smokers, Ex-smoker and Non-smoker lung cancer patients and Control were also compared. The higher CRP level was observed in the smoker, Ex-smoker as compared to non-smoker both in lung cancer patients and control (Fig. 2). The present study indicates that the significant association was found in serum CRP level in Smoker, Ex-smoker and, Non-smoker in lung cancer and control ($p < 0.0001$).

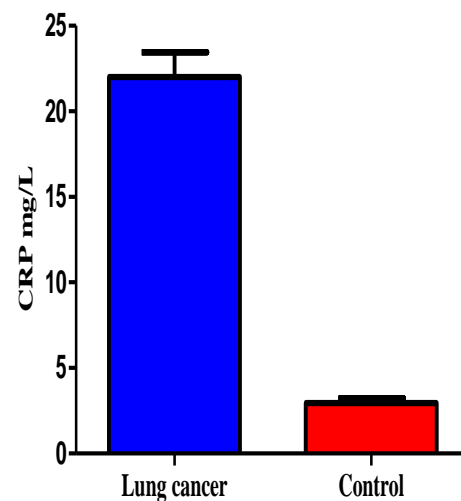


Fig. 1: Serum CRP level in Lung Cancer Patient and Healthy Control

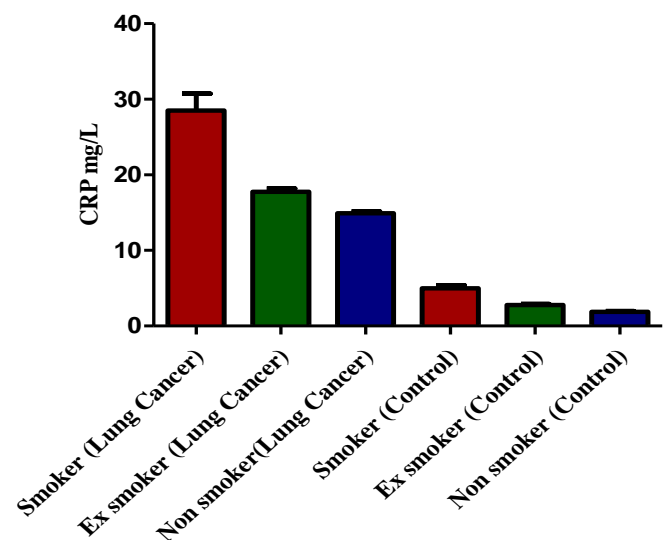


Fig. 2: Serum CRP level in smoker, Ex-smoker and Non-smoker Lung Cancer patient and healthy control

Table 1: Clinical characteristics of Lung Cancer Patients and Healthy Control

Parameters	Lung Cancer (N=40)	Controls (N=30)	P-value
Age	55.73±1.82	53.93±1.82	0.449
Sex			
Male	33(82.5%)	24(80%)	0.771
Female	7(17.5%)	6(20%)	
Height	159.9 ±1.28	158.3±1.38	0.533
Weight	47.58±1.25	55.03±1.70	< 0.0001*
BMI	18.67±0.41	22.06±0.74	< 0.0001*
Smoking History			
Smoker	19(47.5%)	9(30%)	0.2154
Ex- Smoker	8(20%)	5(16.7%)	
Non Smoker	13(37.5%)	16(53.3%)	
Histology			
Adenocarcinoma	19(47.5%)		
Squamous Cell Carcinoma	17(42.5%)	–	–
Small Cell Carcinoma	1(2.5%)		
NSCC	3(7.5%)		
Stage			
I/II	3(7.5%)	–	–
III/IV	37(92.3%)		

DISCUSSION

CRP was discovered in 1930, which is a representative acute-phase reactant, whose level was rapidly increased in response to most of the inflammation [22]. It is considered as one of the most widely used systemic inflammatory markers *in vivo* condition [23]. CRP was reported to be an informative biomarker, which reflects disease progression as well as the efficacy of therapeutic intervention [24]. Serum CRP levels begin to increase within 4-6 h after the onset of inflammation and become at peak concentration at 36-50 h. After the inflammation resolution serum levels, decrease with a half-life of less than 12 h [25]. As tumor growth can cause tissue inflammation around the tumor and hence plasma levels of CRP was increased. The mechanism by which cancer occurs along with increased CRP level is widely known. It has been shown by the previous studies that CRP level was elevated among former smoker and was associated with increased lung cancer risk even among ex-smoker, who had quit smoking for up to 15 years. It has been also found that high CRP levels among current smokers in relation to the amount smoked, which support the notion of a role of inflammatory pathways in tobacco-related lung cancer [15,17]. It has been shown from the previous studies that the serum CRP level was highly elevated in lung cancer patients when compared with healthy control [6,26]. The evidences have indicated that cigarette smoke by itself can also induce pulmonary inflammation [27]. Elevated CRP values were also detected in NSCLC patients with

larger tumor sizes, therefore being both an important staging factor and prognostic factor [12]. Elevated CRP has also been associated with increased weight loss, reduced performance status, increased fatigue and decreased survival [28]. The present study shows that the serum CRP level was higher in lung cancer patients in comparison to healthy control and also the elevated level of CRP was found in smokers as compared to Ex-smoker and Non-smoker in lung cancer patient and healthy control. The significant association between the serum CRP level was found in lung cancer patient as compared to healthy control ($p < 0.0001$) and also significant association were found in smoker, ex-smoker and non-smoker lung cancer patients, when compared with healthy control ($p < 0.0001$). The circulating CRP levels can be used as a useful prognostic predictor for survival in lung cancer. Researchers focused on extending the clinical use of circulating CRP to the prediction of cancer.

CONCLUSIONS

Significant association of serum CRP level between lung cancer patients and healthy controls were found and also significant association between smoker, ex-smoker and non-smoker lung cancer patients and healthy controls were found in this study. The present study concluded that serum CRP level was higher in lung cancer patients, when compared to healthy subjects. The elevated serum CRP level was also found in smoker, when compared with ex-smoker and non-smoker in lung cancer patients

and healthy controls. Serum CRP measurements are simple, rapid, cost-effective. Smoking cessation in patients only reduces; it does not eliminate the risk of lung cancer because inflammation persists even after smoking cessation. Therefore, smoking cessation along with CRP lowering agents may have promising roles for the prevention and therapy of lung cancer.

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