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Association between the serum CRP level and different subtypes in Non-Small Cell Lung Cancer

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Abstract
Background: C-reactive protein (CRP) was discovered in 1930 and is widely used as a sensitive, but nonspecific, marker of systemic inflammation. 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. Increased serum CRP (s-CRP) levels have been reported in many pulmonary disorders, including pneumonia, malignancies, and pulmonary thromboembolism.

Keywords: Serum CRP, TNM staging, Non-Small Cell Lung Cancer, prognostic marker

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].
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.
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.
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. Procalcitonin has been shown to be important in the differential diagnosis of cancer patients with fever and high CRP levels.

Material and methods
Present study was single-center, cross-sectional study, conducted in Department of General Surgery Kanachur Institute of Medical Sciences, Mangalore, India.

Study duration was of 2 years (January 2019- June 2020). Study was approved by institutional ethical committee.

Inclusion criteria

- Newly diagnosed Patients with Non-Small Cell Lung Cancer

Exclusion criteria

- Patients under chemotherapy, radiation therapy, or any history of either use of anti-inflammatory drugs or systemic steroids.
- Presence of inflammatory disease or sepsis.

Written consent was obtained from patients prior to participation in study. Patients demographic profiles, complaints, smoking history, symptoms duration, relevant personal/family history, signs and symptoms, radiographic findings, histopathological subtypes, and clinical staging of lung cancer were noted in detail in proforma.

Routine hematological examinations, sputum for malignant cytology, chest radiology [X-ray, computed tomography (CT) thorax] were done for all patients. Investigations like CT/ultrasound guided fine-needle aspiration cytology (FNAC)/biopsy, pleural fluid malignant cytology, Lymph node biopsy, thoracoscopic biopsy were done when indicated. In selected patients Fiber optic bronchoscopy (FOB) was done for biopsy and bronchial aspirate. On admission CRP levels were measured & correlated with different subtypes in Non-Small Cell Lung Cancer.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Chi-square test to determine the association between different subtypes, tumour size, tumour staging of NSCLC and serum CRP will be done. P value less than 0.5 was considered as statistically significant.

Results

Table 1: Age & gender Distribution

Characteristic	Frequency	Percent
Age (years)		
30 - 45	6	15.8
46 - 60	18	47.3
≥ 61	14	36.8
Gender		
Male	21	57.6
Female	17	42.4

Table 2: Presenting complaints amongst the study population

Chief complaint	Frequency	Per cent
Breathlessness	8	21.1
Cough with breathlessness	7	18.4
Chest pain	5	13.2
Cough with expectoration	4	10.5
Chest pain and breathlessness	3	7.9
Cough	3	7.9
Cough and Haemoptysis	3	7.9
Cough and chest pain	1	2.6
Cough and weakness	1	2.6
Cough with weight loss	1	2.6
Generalized weakness	1	2.6
Weight loss	1	2.6

Table 3: TNM staging

TNM staging	Frequency	Per cent
T		
T1	5	13.2
T2	7	18.4
T3	17	44.7
T4	9	23.7
N		
N0	2	5.3
N1	9	23.7
N2	18	47.4
N3	7	18.4
Nx	2	5.3
M		
M0	23	60.5
M1	15	39.5

Table 4: Serum CRP levels and Histopathology of Non-Smal Cell Lung Cancer

Diagnosis	N	Minimum	Maximum	Median	IQR
Adenocarcinoma	15	0.50	90.86	15.11	27.46
Bronchogenic carcinoma	2	29.85	57.66	43.75	-
Squamous cell carcinoma	21	0.50	283.68	41.84	67.64

Table 5: Diagnosis and stages.

Diagnosis	Stage group				Total
	Stage I (n=1)	Stage II (n=6)	Stage III (n=16)	Stage IV (n=15)	
Adenocarcinoma	0	3 (50 %)	5 (31.3 %)	7 (46.7 %)	15 (39.5 %)
Bronchogenic carcinoma	0	0	2 (12.5 %)	0	2 (5.3 %)
Squamous cell carcinoma	1 (100 %)	3 (50 %)	9 (56.3 %)	8 (53.3 %)	21 (55.3 %)
Total	1	6	16	15	38
Chi-square value- 4.18					
p value- 0.65					

Discussion

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 been shown to have higher CRP concentrations than healthy controls and participants with some benign diseases [11].

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.* [12], and it was not known whether the 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. Second, CRP could be an indicator of an immune response to tumor antigens. 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. And cancer cell lines have been shown to secrete IL6 and IL8, which in turn induce the production of CRP. 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.

Conclusion

There is no association between serum CRP with different subtypes, tumour size and TNM staging in Non-Small Cell Lung Cancer. Hence, serum CRP is not a useful prognostic indicator in the Non-Small Cell Lung Cancer.

Conflict of Interest: None to declare

Source of funding: Nil

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