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Title page

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Study of 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) is a commonly used marker of systemic inflammation. The elevated levels of CRP are associated with an increased risk of all-cancer, lung cancer, breast, prostate and colorectal cancer. Present study was aimed to study of association between the serum CRP level and different subtypes in Non-Small Cell Lung Cancer.**Material and Methods:**Present study was single-center, cross-sectional study, conducted newly diagnosed patients with non-small cell lung cancer. On admission CRP levels were measured & correlated with different subtypes in Non-Small Cell Lung Cancer.**Results:**Out of 38 subjects, 18 (47.3%) subjects were aged 46-60 & male (57.6%). Breathlessness was the most common presenting symptom (21.2%), followed by cough with breathlessness (18.4%). Squamous Cell Carcinoma was the most common histopathology (55.3%) among the Non-Small Cell Lung Cancer patients. As per TNM classification 16 (42.1%) had stage III followed by 15 (39.5%) had stage IV, 6 (15.8%) had stage II and 1 (2.6%) had stage I. CRP levels were higher in Bronchogenic carcinoma (43.75) followed by Squamous cell carcinoma (41.84) and Adenocarcinoma (15.11).**Conclusion:**There is no association between serum CRP with different subtypes, tumour size and TNM staging in

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Non-Small Cell Lung Cancer. Hence, serum CRP is not a useful prognostic indicator in the Non-Small Cell Lung Cancer.

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

INTRODUCTION

C-reactive protein (CRP) is a commonly used marker of systemic inflammation, which was produced in the early 1930s1. It is a sensitive marker but is not specific for any particular cause of inflammation1. Most lung cancer cases (85%) are categorized as Non-Small Cell Lung Cancer (NSCLC), with the remaining cases constituting Small Cell Lung Cancer (SCLC)1.

As an Acute Phase Reactant (APR), it is considered a prototype and is found to exponentially increase when there is an underlying inflammatory stimulus2. The cellular effectors of inflammation are integral parts of the tumour local environment. Despite advances in early detection and diverse treatments, the outcomes of NSCLC patients are still poor, with the 5-year overall survival rate being 18.2 %3.

The elevated levels of CRP are associated with an increased risk of all-cancer, lung cancer, breast, prostate and colorectal cancer3. Studies have shown that there is a correlation between Cancer Cachexia, Disease extent and Recurrence in cases of advanced4. There are several other markers of inflammation found to be associated with lung carcinoma such as Interleukin 6 (IL-6) and Interleukin 8 (IL-8).5 Present study was aimed to study of association between the serum CRP level and different subtypes in Non-Small Cell Lung Cancer.

MATERIAL AND METHODS

Present study was single-center, cross-sectional study, conducted in Department of General Surgery and Department of Pulmonology, Justice K S Hegde Charitable Hospital, attached to K.S.Hegde Medical Academy, a unit of Nitte (Deemed to be University) Deralakatte, 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

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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

Out of 38 subjects, 18 (47.3%) subjects were aged 46-60 yrs followed by 14 (36.8%) subjects were ≥ 61 yrs. A slight male predominance (57.6%) was noted in the study population,

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

Breathlessness was the most common presenting symptom (21.2%), followed by cough with breathlessness (18.4%).

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

All the patients with clinical suspicion of Carcinoma of the lung underwent Endoscopic USG image-guided or Bronchoscopy guided biopsy. Amongst this, it was observed that Squamous

Cell Carcinoma was the most common histopathology (55.3%) among the Non-Small Cell Lung Cancer patients.

When the TNM staging was studied in the population, it was found that T3 was the most common tumour size staging i.e in 44.7%. Out of the 38 subjects, 18(47.4%) subjects had N2 staging followed by 9(23.7%) had N1 staging. When the study population was evaluated for metastasis, it was found that 15 of the 38 study participants (39.5%) had metastasis. (M1 staging.) Considering the TNM classification of each of the study subjects, the staging was done. Out of 38 (100%) subjects, 16 (42.1%) had stage III followed by 15 (39.5%) had stage IV, 6 (15.8%) had stage II and 1 (2.6%) had stage I (Figure 21).

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

In this study, the serum CRP levels in all patients with Non-Small Cell Lung Cancer were studied. It was observed that the median CRP levels were higher in Bronchogenic carcinoma (43.75) followed by Squamous cell carcinoma (41.84) and Adenocarcinoma (15.11)

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

Median CRP levels were higher in stage III group (35.84) followed by stage IV (18.07) and stage II (17.29). Out of 16 subjects with stage III, 9 (56.3%) were having SCC and 5 (31.1%) were having adenocarcinoma. Similarly, out of 15 subjects in stage IV, 8 (53.3%) were having SCC and 7 (46.7%) were having Adenocarcinoma . Chi-square test was applied to associate the diagnosis with stages. Chi-square test showed no significant association between diagnosis and stages ($\chi 2=4.18$; $p=0.65$)

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

Non-Small Cell Lung Cancer is more common than the Small Cell variant, and it accounts for approximately 85% of all the cases of lung carcinoma.[6] Some studies have shown that elevated serum CRP levels can be associated with the reduced survival in patients with NSCLC.[7]CRP is a marker of systemic inflammation, and its been implicated in the aetiopathogenesis of NSCLC. In this study, the median CRP levels were found to be highest for Bronchogenic Carcinoma, followed by Adenocarcinoma and Squamous Cell Carcinoma.

In a study done by Aref H, et al.[1] , it was observed that serum CRP levels did not correlate with the histopathological type of NSCLC. When we consider the serum CRP levels and the staging, it was found that median CRP levels were highest in stage III. This indicates that CRP could be an indicator of progressive/advanced disease.

In the study done by Aref H, et al.[1] , it was found that there was a positive correlation between tumour size and staging with serum CRP levels. However, in a study done by Jing Z, et al.[8]the expression of SF (Serum Ferritin), CEA (Carcino Embryonic Antigen) and CRP in the adenocarcinoma group was higher than that in the squamous cell carcinoma group. The difference is statistically significant ($P<0.01$). When the serum CEA, SF and CRP levels were used alone for diagnosis of NSCLC, CRP had the best diagnostic value. The combination detection of CRP, CEA and SF can increase the early diagnostic accuracy of NSCLC, so as to provide basis for clinical treatment. Jing X, et al.[9]did a study in the Association between serum C-reactive protein value and prognosis of patients with Non-Small Cell Lung Cancer. This meta-analysis clarified that CRP is an independent prognostic factor for patients with NSCLC.

In this study, we observed that there was a slight male predominance amongst the study population. In a study done by Shrotriya S, et al.[10] it was observed that two thirds of the tested solid tumour population had a high serum CRP level that was more common in males. However, in a study done by Seigel, et al.[11] it was observed that the disease is more predominant in women, and it is also true for the number of deaths due to non-small cell lung carcinoma.

In this study, the majority of the patients belonged to the age group of 46-60 years. The median age at diagnosis of Non-Small Cell Lung Cancer (NSCLC) is 70 years; a subset of patients with NSCLC present at a younger age (<40 years). The findings of the study by Thomas A, et al.[12]corroborates with the findings of our study.

NSCLC unlike its Small Cell counterpart is often occult, with patients being asymptomatic in the initial stages of the disease. By the time the disease manifests itself, we often find that it is too far gone. In our study, we observed that the most common presenting complaint was breathlessness, followed by cough with breathlessness. In a study done by Ellis PA, et al.[13] the findings were similar to our study. According to a study done by Vijayvergia N, et al.,[14] cough and breathlessness were the most common respiratory symptoms amongst Non-Small Cell Lung Cancer. In a study done by Kocher, et al.,[15] cough was seen in 50% to 75% of patients, is the most common symptom, followed by haemoptysis, chest pain, and dyspnoea.

NSCLC can be of different histopathological variants. Amongst these, we found Squamous cell carcinoma to be the most common variant in our study. In a study done by Ho C, et al.,[16] 63% of the cases were Non-squamous in nature, which contradicts the findings in our study. In a study done by Galateau-Salle F, et al.,[17]adenocarcinoma was the most common variant of NSCLC. Aref H et al.[1] , did a study of CRP evaluation in Non-Small Cell Lung Cancer. They concluded that different subtypes of NSCLC were compared concerning serum CRP and the results had no statistical significance.

When considering the TNM staging of the patients in our study, we found that majority of the study population were in advanced stages (III and IV). This is like the statistics compiled by WHO[52]. In a study done by Martini N, et al.,[18] the incidence of NSCLC is 10%, which indicates that patients seldom present on the stage of localised disease.

In this study, when the CRP was analysed for association with histopathology and staging, there was no statistical significance obtained. This contradicts the findings of Aref H et al.,[1] where they found that there is a positive association between serum CRP and staging of the disease, which indicates that it's a potential prognostic marker in NSCLC.

Several studies have indicated that pre-treatment high CRP is a significant prognostic indicator in patients with esophageal carcinoma,[19] hepatocellular carcinoma,[20] and Non-Small Cell Lung Cancer (NSCLC). Hara M, et al.[21]did a study in Preoperative serum C-reactive protein level Non-Small Cell Lung Cancer. They concluded that the preoperative serum CRP level is an independent and significant indicator predictive of a poor prognosis in patients with NSCLC.In a study done by Xiao X, et al.,[22] it shows that the higher level of CRP is associated with poor prognosis and hence can be used as an independent prognostic factor in patients with NSCLC chemotherapy.

In a study done by Lee JG, et al.,[23] they reported an association between preoperative serum CRP levels and pathologic parameters such as tumour size and lymphovascular invasion in patients with NSCLC. Govindan R et al.,[24] did a study on treatment approaches in patients with advanced Non-Small Cell Lung Cancer and poor performance status. They concluded that the cellular effectors of inflammation are integral parts of the tumor local environment.

CRP, as mentioned earlier, is a marker of inflammation, and is non-specific. It is produced by the hepatocytes, and this production is stimulated by the pro-inflammatory cytokine IL6.[21] Despite its strong association with acute inflammation, there have been several studies that have studied the relationship between CRP and its role in malignancies. Below, a few theories have been mentioned:-

1. The growth of the tumour cells insights an inflammatory response within the surrounding normal tissue as part of the host's defence mechanism. The abnormal tumour cells release several pro-inflammatory cytokines and chemoattractants, due to which CRP might also be stimulated from the hepatocytes.
2. The abnormally proliferating tumour cells express several antigens on the cell membrane and nucleus. These antigens generate a humoral immune response, towards which antibodies will be produced. In this process, there might be an increase in CRP.
3. The tumour cell itself be the site of production of pro-inflammatory cytokines, which could be the reason for high CRP values in patients with malignancy.

Carcinoma lung cancer patients presents with signs and symptoms similar to TB or COPD leading to patients presenting late to the specialized centers. A sincere effort is needed to find out the etiology, prevent the risk factors, to diagnose early and treat effectively so that patients morbidities can be reduced.

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
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