Section: Respiratory Medicine

Original Research Article

A PROSPECTIVE STUDY TO EVALUATE ADVANCE LUNG CANCER INFLAMMATORY INDEX (ALI) AS A PROGNOSTIC MARKER TO PREDICT SURVIVAL OUTCOME IN PATIENTS WITH LUNG CANCER

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Abstract

Background: Systemic inflammation has been linked with cancer development, cancer cachexia and poor outcome. Recently, the advanced lung cancer inflammation index (ALI) was developed as a new prognostic tool for patients with advanced lung cancer. The aim of this study was to explore the relationship between ALI and the prognosis of lung cancer in Indian scenario. **Materials & Methods:** A total of sixty patients with Non-Small cell lung cancer who diagnosed at our institution between June 2018 to May 2019 were included. The ALI score was calculated as body mass index serum albumin/neutrophil to lymphocyte ratio. Patients were divided into low inflammation (ALI≥18) and high inflammation (ALI<18) groups. Descriptive and Inferential statistical analysis has been carried out in the present study using computer software (SPSS Trial version 23 and primer). **Results:** Among 60 patients mean age was 60.17±9.87 years, 90% were male, 53.33% had Squamous cell carcinoma. Patients with an ALI score of <18 suggesting high systemic inflammation were significantly more likely to have more than 2 sites of metastatic disease, have poor performance status and less likely to receive any chemotherapy. Their mean overall survival was 69.91±52.375 days and 179.04±5.004 days in patients with ALI >18 (P < 0.001). **Conclusion:** ALI (<18) at diagnosis is an independent marker of poor outcome in patients with advanced NSCLC.

INTRODUCTION

Lung cancer is the most commonly diagnosed and fatal cancer annually since 1985 in the world. In India about 67,795 cases of lung cancer cases are reported annually (5.9% of total cancer cases), i.e. the fourth leading cause of cancer and the third leading cause of cancer deaths in India (8.1%). It is the malignancy with the highest mortality worldwide, being the only one whose incidence of death has progressively increased despite improved and more aggressive therapy in recent years. The mean five-year survival ranges from 13% to 21% and from 7% to 10% in developed and in developing countries, respectively.

Inflammation is recognized both as a condition that leads to cancer development and also as a condition that arises due to oncogenic changes in cancer cells.[1] The six hallmarks of cancer, distinctive and complimentary capabilities that enable tumour growth and metastatic dissemination are sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis and activating invasion and metastasis. Inflammation has been described as the underlying or enabling characteristic that promotes these hallmarks of cancer.[2]

Systemic inflammation besides promoting tumour growth has also been shown to be responsible for many cancer related symptoms including cancer cachexia, anorexia, pain, debilitation and shortened survival.[3]

Previous studies have identified several inflammation/nutrition biomarkers as prognostic factors in patients with non-small cell lung cancer (NSCLC); these include body mass index (BMI)[4,5], C-reactive protein (CRP),[6-8] CRP-to-albumin(ALB) ratio (CAR),[9,10] absolute white cell and its components (neutrophils, neutrophils/ lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR)[11] and red cell distribution width (RDW).[12]

In 2013, Jafri et al[13] developed a new prognostic index termed Advanced Lung Cancer Inflammation Index (ALI) for patients with advanced lung cancer including small-cell lung cancer. ALI incorporates both inflammation and nutrition factors, the same as

GPS, and consists of Body Mass Index (BMI), albumin, and NLR. Its utility has been reported for patients with oesophageal cancer, small-cell lung cancer, and malignant lymphoma.[14 -16]

The aim of the present study was to evaluate degree of systemic inflammation at the time of diagnosis in patients with advanced NSCLC as a prognostic marker for outcome. For this purpose, we use a simple index based on patient's height, weight, serum albumin and NLR from the time of diagnosis called as "Advanced lung cancer inflammation index (ALI)". Therefore, identifying an effective prognostic index for patient survival could help clinicians adopt better preventive and therapeutic treatments, which could further reduce cancer mortality.

MATERIALS AND METHODS

A total of 60 patients, including both males and females, admitted during November 2018 to May 2019 at Department of Respiratory Medicine, SMS Medical College, Jaipur, with a diagnosis of advanced lung cancer presented with stage III and stage IV, were included in the study. Patients with a prior history of non-small cell lung cancer presenting with relapse, prior history of other cancers in preceding 5 years and those with incomplete medical information or follow up were not included in study. Complete blood count, Absolute neutrophil count, Absolute lymphocyte count and Serum albumin level were accessed within 2 weeks of diagnosis from routine blood investigation. Weight and Height of each patient were recorded.

According to 8th TNM staging patients were stratified in locally advanced (stage III) or metastatic (stage IV) NSCLC. For all the patients at the time of presentation ALI were calculated by

ALI = (BMI) x(Alb) / NLR

Where: Body mass index (BMI) =weight (lb)/ height (in)^2 ×703, Alb-serum albumin g/dl, Neutrophil lymphocyte ratio (NLR) = ANC/ALC,ANC – Absolute neutrophil count

ALC - Absolute lymphocyte count

Depending upon ALI score patients were further divided in two group ALI<18 &ALI≥18.First response assessment was performed after 3rd cycle of chemotherapy containing Carboplatin and Paclitaxel. All patients were followed for 180 days after that statistical evaluation performed.

Statistical Analysis

Descriptive and Inferential statistical analysis has been carried out in the present study using computer software (SPSS Trial version 23 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analysed by using chi square test. The difference in means among the groups was analysed using the Student T test Correlation between quantitative outcomes was assessed using Pearson correlation coefficient. Significance level for tests was determined as 95% (P< 0.05).

RESULTS

All 60 patients were followed up to six months (180 days). Patient's characteristics are shown in Table no 1.

Median age was 61 years old with (range from 42 to 83 years).90% of patients were male. Most of the patients (91.66%) were smoker. The median Body mass index was 18.550 kg/m2 with 50% patients were underweight and 50% were normal weight. In order to get an estimate of on-going systemic inflammation at the time of diagnosis we calculated ALI for each patient using the formula described above. Range of ALI was 1.94- 43.42. Patients were then divided into two groups, those with ALI of<18 (more inflammation) and those with ALI of ≥ 18 (less inflammation). There was no significant difference sex and tumour histology between the two groups.

Our study show that squamous cell carcinoma was the most common histological type in both the group (54.54% in group ALI<18 &51.85% in group ALI≥18) followed by NSCLC not otherwise specified (NOS), (27.27% in group ALI<18 & 18.51 in group ALI≥18) [table 2].

Different sites of metastatic disease included lung, liver, brain, bones, adrenal glands, spleen and retroperitoneal lymph nodes and each was considered a separate metastatic site. In group ALI<18, 54.55% subject shows > 2 metastasis site while in group ALI ≥18, 96.30% patients had either one or no metastasis (table 3). ECOG performance in most of the patient [96.97%] was 2-4 in ALI<18 group while in group ALI ≥18 most of the patient [59.26%] belonged to ECOG score 0-1 [table 4].

The median serum albumin level was3.55 gm/dl with a range of 2.4-4.75gm/dl. Our study shows that high ANC\ALC ratio mean more inflammation in group ALI<18 patients. Mean ANC\ALC ratio was 6.706± 3.5101 in group ALI<18 and 3.068± 0.7403 in group ALI ≥18. Hence, significant difference of ANC\ALC level observed among the study groups (P value < 0.001) [table 5].

About a quarter (23.33%) of all patients could not receive any chemotherapy due to poor PS. 61.66% patients received at least 3 cycle of chemotherapy and 25% received six complete cycle of chemotherapy. Before first response assessment 26.66% patients were expired. At first response assessment 36.66% had response to chemotherapy, 11.66% had stable disease and 6.66% had progression of disease and 11.66% had decline in PS making them ineligible for further chemotherapy [figure 1].

Compared to patients with ALI score of ≥ 18 patients with an ALI score of < 18 were significantly more likely to have more than 2 sites of metastatic disease at the time of diagnosis (P = 0.03), have poor PS (P = 0.000), less likely to receive any chemotherapy (P <0.008) and very low response to chemotherapy (P <

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0.00001). They also did worse in terms of Overall Survival (OS). Patients with ALI of <18 had a mean OS of 69.91 day with a standard deviation of 52.375 day. Patients with ALI of > 18 had a mean OS of 179.04 days with a standard deviation of 5.004 days. Difference in OS was highly significant between two groups (P < 0.0001) [table 6].

A significant positive correlation existed between the survival days and ALI (r= 0.76good positive correlation p < 0.01).by using Pearson's correlation coefficient [figure 2].

Table 1: Demographic profile of Study Population

Demographic profile	ALI<18 (N=33)	ALI ≥18 (N=27)	Total (N=60)	P Value LS
Age (yrs)				
Mean±SD	62.61±9.549	57.19±9.56	60.17±9.87	0.03*
Gender				
Female	3 (9.09%)	3 (11.11%)	6 (10%)	0.863
Male	30 (90.91%)	24 (88.89%)	54 (90%)	
Smoking (pack years)				
Non smoker	1 (3.03%)	4 (14.81%)	5 (8.33%)	>0.05
<20	3 (9.09%)	3 (11.11%)	6 (10%)	
20-40	18 (54.54%)	13 (48.14%)	31 (51.66%)	
>40	11 (33.33%)	7 (25.82%)	18 (30%)	
BMI (kg/m^2)				
<18.5 (underweight)	24 (72.73%)	6 (22.22%)	30 (50%)	<0.05*
18.5-24.99 (normal)	9 (27.27%)	21 (77.78%)	30 (50%	

Table 2: Histologically distribution of study subject

Pathological type	ALI<18		ALI≥18		
	No	%	No	%	Total
Adenocarcinoma	3	9.09	6	22.22	9
Squamous cell carcinoma	18	54.54	14	51.85	32
NSCLC NOS	9	27.27	5	18.51	14
Large cell carcinoma	1	3.03	0		1
Poorly differentiate carcinoma	2	6.06	2	7.40	4

NSCLC NOS: NSCLC not otherwise specified

Table 3: Number of metastasis site in study group

Number of metastasis site	ALI<18		ALI ≥18		Total	P Value LS
	No	%	No	%		
0 to 1	15	45.45	26	96.30	41	0.03S
>2	18	54.55	1	3.70	19	

Table 4: ECOG score in study subject

ECOG Score	ALI<18		ALI ≥18		Total
	No	%	No	%	
0 – 1	1	3.03	16	59.26	17
2- 4	32	96.97	11	40.74	43

Chi-square = 20.436 with 1 degree of freedom; P = 0.00**0**

Table 5: ANC\ALC ratio in study subject

ANC\ALC					
Group	Number	Mean	Std. Deviation	Median	
ALI<18	33	6.706	3.5101	5.700	<0.001
ALI ≥18	27	3.068	.7403	3.043	
Total	60	5.069	3.2025	4.070	

Table 6: Correlation of survival days with serum albumin BMI ANC/ALC and ALI

Correlations					
		Serum albumin	BMI	ANC\ALC	ALI
Survival days	Pearson Correlation	0.420**	0.551**	-0.549**	.760**
	Sig.(2-tailed)	.001	<0.001S	<0.001S	<0.001S
	N	60	60	60	60
**. Correlation is significant at the 0.01 level (2-tailed).					

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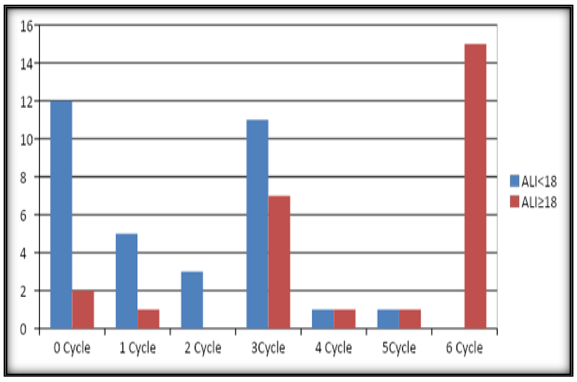

Figure 1: No of chemotherapy received by study object

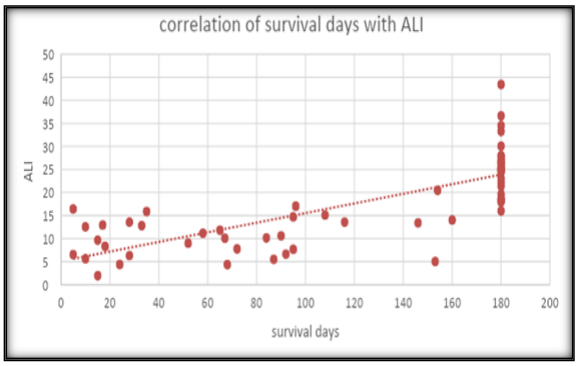

Figure 2: Correlation of survival days with ALI

DISCUSSION

Cancer and inflammation are closely linked and many inflammatory conditions increase the risk of cancer development like inflammatory bowel disease and increased risk of colorectal cancer, hemochromatosis and liver cancer [17] and Sjogren's syndrome and lymphoma.[18]

To our knowledge, this is the first prospective study to investigate the role of ALI as a prognostic indicator in NSCLC patients. Similar to previous study[13] in our study there was no difference in ALI score based on tumour histology suggesting that both squamous cell carcinoma and other histology type generate similar degree of systemic inflammation.

Two meta-analyses demonstrated that an elevated NLR was a predictor of poor overall survival in patients with lung cancer.[19,20] The exact underlying mechanisms for the association of elevated NLR with the prediction of poor survival in patients with NSCLC have not been determined. An elevated NLR implies an increased neutrophil count and/or a decreased lymphocyte count as well as relative lymphopenia. Neutrophils produce cytokines, which inhibit lymphocyte-mediated immune activity comprised of natural killer T cells or activated T cells.[15,16] A decreased lymphocyte count has been demonstrated as a biomarker of poor survival for patients with terminal cancer due to the key role of lymphocytes in killing cancer cells and regulating the proliferation, apoptosis, angiogenesis and metastasis of cancer by secreting cytokines.[21] Therefore, NLR might serve as a host marker of tumour defence, which inhibits tumour cell proliferation and migration. In the present study, similar to other studies[13,22–26] low ALI group patients had more inflammation and high ALI group had less inflammation. The importance of BMI with regard to cancer progression can have different implications. Previous published studies have shown that BMI is a predictor of survival in several cancers, such as breast cancer, gynaecological cancer, and lymphoma.[27-29] Tewari et al.[30] and Nakagawa et al.[31] reported that, in patients with NSCLC, low BMI, a surrogate for impaired nutrition, was a negative predictor of long-term survival in resected NSCLC. Similar to other studies,[13,22–26] our studies show that a greater number of patients in low ALI group were underweight and in high ALI group had normal weight.

ALB is also a good index for indicating nutritional status, and malnutrition has been reported to be associated with survival in patients having surgery for NSCLC.[32,33] The underlying mechanism of this effect is unknown in detail, but impaired immune function due to nutritional depletion might lead to the inability of the body's immune system to remove the cancer. Malnutrition and inflammation have been reported to suppress albumin synthesis.[34] Therefore, hypoalbuminaemia might serve as a clinically valuable marker of inflammation in addition to malnutrition in patients with NSCLC. Similar to previous studies,[13,22–26] current study observed that a greater number of patients in low ALI group were had hypoalbuminaemia. Combined with the BMI, serum ALB, and NLR, we found that the ALI serves as a more comprehensive indicator of outcome, and thus plays an important role as a predictor of survival. Furthermore, our study also showed that low ALI was related >2 metastatic sites (54.54%), poor ECOG performance score, receive no chemotherapy which was also similar to previous studies.[13,22-26]

In our study we observed that in group ALI<18 mean survival days was 69.91±52.375 which was similar to previous study[13] in which ALI <18 had a median overall survival of 3.4 months.

Limitations

Limitations of this study include its nature as a single institute prospective examination and the small patient population. Accumulation of additional cases is necessary to clarify the utility of ALI as a prognostic factor in patients with lung cancer. Second, this study focused on the pre-treatment ALI and NLR, which may be affected by other factors like infections or cancer-related complications. Also, ALI is a continuous variable hence there may be little difference between ALI of 17 and 19 though they fall on the side of high risk and low risk respectively based on Jafri et al. Patients height, weight, albumin, ANC and ALC were not necessarily from the same date though most were within two weeks of diagnosis.

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CONCLUSION

ALI has the advantage of being simple to measure, routinely available and well standardized. In conclusion, we concluded that lung cancer patients with a low ALI score have poor survival outcomes and had a shorter overall Survival. Therefore, pre-treatment ALI may act as a valuable candidate with a predictive power in lung cancer and should be considered for routine clinical use.

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