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Diagnostic Values of Tumour Marker CA-125 in Lung Cancer

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Abstract

Lung cancer is the leading cause of cancer death for both men and women and accounts for 29% of all cancer death. The use of tumour markers in oncology practice may reflect both stage of the disease and prognosis. Cancer antigen, CA-125 is a high molecular glycoprotein produced by normal cells derived from the celomic epithelium (fallopian tubes, endometrium, endocervix, peritoneum, pleura, and pericardium). CA-125 is elevated in carcinomas of ovary, lung, endometrial, pancreas, breast and colon. The objective of the study was to estimate serum levels of CA-125 in lung cancer patients, normal healthy individuals and in patients with benign lung diseases. Methodology: Fifty newly diagnosed lung cancer patients who attended Radiotherapy OPD and/or admitted in the Radiotherapy ward, RIMS, Imphal were selected as cases. Control group consisted each of a group of 50 patients with benign lung diseases and a group of 50 normal subjects of comparable age. The study was carried out from October 2018 to September 2020. Laboratory evaluation of serum CA-125 was performed by ELISA. Results: Serum CA-125 level was significantly higher in lung cancer patients (43.17 ± 20.49 U/ml) as compared to controls (normal healthy individuals-22.34 ± 3.58 U/ml and benign lung diseases- 23.94 ± 4.10 U/ml). Also the level is highest in Stage IV (55.64±12.94 U/ml), followed by Stage III (43.31±17.94 U/ml), Stage II (31.66±21.13 U/ml) and Stage I (26.68±23.29 U/ml). Conclusion: Serum CA-125 level might be a valuable biochemical index in the diagnosis of lung cancer. This may be useful in patients in whom tumour cannot be visualized by bronchofibroscopy or to rule out false positive cases.

Keywords: Bronchofibroscopy, CA-125, ELISA, Oncology, Tumour Markers

Introduction

Lung cancer is the leading cause of cancer death for both men and women and accounts for 29 % of all cancer death (31% in males and 26% in females) in the world [1,2]. Some ongoing diagnostic tools at clinics include CT scans, bronchoscopy and sputum analysis, none of which turns out to be effective in early diagnosis of lung cancer [3]. Detection of lung cancer at an early stage rather than at a symptomatic advanced stage is also increasing, suggesting that there are increasing diagnostic demands for small peripheral lung lesions. The development of new molecular diagnostics, including next generation sequencing, companion diagnostics that accompany development of new anti-cancer drugs, and re-biopsy for application of new therapeutic modality accelerate the development of lung cancer diagnostic [4]. Cancer antigen, CA-125 is associated with 80% of non-mucinous ovarian carcinomas and is elevated in other cancers including lung, endometrial, pancreas, breast and colon etc [5]. The aim of this study is to estimate serum levels of CA-125 in lung cancer patients, normal healthy individuals and in patients with benign lung diseases.

Materials And Methods:

The cross-sectional study was carried out in the Department of Biochemistry in collaboration with the Department of Radiotherapy, Regional Institute of Medical Sciences, Imphal from October 2018 to September 2020. Cases consisted of 50 newly diagnosed lung cancer patients who attended Radiotherapy OPD and/or admitted in the Radiotherapy ward, RIMS, Imphal and two control groups who are age and sex matched: one group of 50 patients with benign lung diseases and another group of 50 normal healthy subjects. The study was approved by Research Ethics Board, RIMS and written informed consent were taken from all the participants. Patients with lung malignancy confirmed by computed tomography guided fine needle aspiration cytology (FNAC) of peripheral lymph node were included. Patients with history of cancers in other organs, hepatic disease, acute infection/inflammatory conditions and patients who had received radiation or chemotherapy before were excluded from the study. Each individual enrolled in the study has undergone a detailed history, clinical and laboratory examinations. Laboratory evaluation of CA-125 was performed by Enzyme Linked Immunosorbent Assay (ELISA) by using commercially available ELISA kit procured from CALBIOTECH company, USA.

Statistical analysis was performed using SPSS software 19 version. Results were reported as mean ± SD (standard deviation) for quantitative variables and number of cases along with percentages for the categorical/qualitative variables. The group's means were compared by F-test (commonly known as ANOVA) and χ^2-test (or Fisher's Exact Test, if necessary) for categorical variables. Strength of association between the tumour markers was estimated by Pearson's bivariate correlation coefficient "r" to establish relationship between the tumour markers. Cut-off levels for serum CA-125 was calculated for lung cancer. Sensitivity and specificity of the marker was calculated through receiver operating characteristics (ROC) curve. All comparisons were two-sided, and all *p* values less than 0.05 and 0.01 were used as the cut-off values for significance and highly significance respectively.

Results

Table-1 shows the distribution of the study subjects over the three groups considered according to their socio-demographic and behavioural factors. It is seen that number of males was higher than females among the cases and normal healthy subjects. However, the sex composition of one group is almost similar to the sex composition of the other groups (χ^2 =0.667, p=0.414). Hindu comprises the highest number in each group and there was no significant difference among the groups as evident by p=0.129. In the study sample, the number of urban subjects was more than that of rural subjects. However, no significant difference is observed as evident by p=0.775. Twenty eight cases gave family history of lung cancer while the remaining 22 did not have the history. But there was no significant variation as shown by p=0.248.

Smoking pattern was quite different (p<0.001) as the percentage of non-smokers is more in the benign lung disease and normal healthy group while more of current smokers and ex-smokers are present in the lung cancer group.

Table 2 shows the comparison of parameters considered in the present study. In the study sample, the most common histological type was adenocarcinoma (70%), followed by squamous cell carcinoma (16%), large cell carcinoma (10%), and small cell lung cancer (4%). Majority of the case patients have stage III tumours (38%), followed by stage IV (34%), stage I (16%) and stage II (12%). The mean CA-125 level is highest in the case group (43.17±20.49 U/ml) followed by benign lung disease group (23.94±4.10 U/ml) and the lowest value is found in normal healthy group (22.34±3.58 U/ml). These differences are statistically significant as evident by p-value (<0.001).

It is observed from Table 3 that the serum level of CA-125 is highest in Stage IV (55.64±12.94 U/ml), followed by Stage III (43.31±17.94 U/ml), Stage II (31.66±21.13 U/ml) and Stage I (26.68±23.29 U/ml). The difference is also found to be statistically significant as p<0.05.

Table 4 shows that the highest level of serum CA-125 was found in adenocarcinoma (54.71±10.07 U/ml), followed by small cell lung cancer (27.00±9.89 U/ml), squamous cell carcinoma (18.56±13.95 U/ml) and large cell carcinoma (11.00±1.36 U/ml).

It is evident from Table-5 that CA-125 is a sensitive marker for detecting lung cancer as the area under the ROC curve for CA-125 is 0.924.

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Table-1: Baseline socio-demographic characteristics of the study subjects

Parameters		Case patients n=50 No. (%)	Control subjects n=100		χ^2-value	df	p-value
			Benign lung disease group n=50 No. (%)	Normal Healthy subjects n=50 No. (%)			
Sex	Male	35(70.0)	24 (48.0)	27(54.0)	0.667	2	0.414
	Female	15(30.0)	26(52.0)	23(46.0)			
Inhabitance	Urban	30(60)	30(60)	34(68)	0.509	2	0.775
	Rural	20(40)	20(40)	16(32)			
Family history of lung cancer	Yes	28(56)	20(40)	16(32)	2.786	2	0.248
	No	22(44)	30(60)	34(68)			
Smoking	Current	21(42)	3(6)	6(12)	43.808	4	<0.001
	Non-smoker	9(18)	40(80)	29(58)			
	Ex-smoker	20(40)	7(14)	15(30)			

Table-2: Group wise comparison of mean ± SD of clinical and laboratory parameters

Parameters	Case patients n=50	Control subjects n=100		F-Value	p-value
		Benign lung disease group n=50	Normal Healthy subjects n=50		
Age (years) Mean ± SD	71.76 ± 8.70	71.14 ± 8.10	70.08 ± 4.94	-	0.489

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BMI (kg/m^2) Mean ± SD		19.45 ± 1.54	19.69 ± 0.81	21.82 ± 0.83	4.674	0.032
Histology No. (%)	AC	35 (70)	-	-	-	-
	SCC	8 (16)	-	-	-	-
	LCC	5 (10)	-	-	-	-
	SCLC	2 (4)	-	-	-	-
Tumour stages No. (%)	I	8 (16)	-	-	-	-
	II	6 (12)	-	-	-	-
	III	19 (38)	-	-	-	-
	IV	17 (34)	-	-	-	-
CA-125 (U/ml) Mean ± SD		43.17 ± 20.49	23.94 ± 4.10	22.34 ± 3.58	7.11	<0.001

(AC - Adenocarcinoma, SCC - Squamous cell carcinoma, LCC - Large cell carcinoma, SCLC- Small cell lung cancer)

Table 3: Serum levels of CA-125 in different stages of lung cancer

Group	CA-125 U/ml Mean ± SD
Lung cancer Stage I (n=8)	26.68 ± 23.29*
Lung cancer Stage II (n=6)	31.66 ± 21.13*
Lung cancer Stage III (n=19)	43.31 ± 17.94*
Lung cancer Stage IV (n=17)	55.64 ± 12.94*

*$p < 0.05$

Table-4: Levels of CA-125 in serum of patients with lung cancer depending on their histology

Group	CA-125 U/ml (Mean±SD)
Adenocarcinoma (n=35)	54.71 ±10.07*
Squamous cell carcinoma (n=8)	18.56 ± 13.95
Large cell carcinoma (n=5)	11.00 ± 1.36
Small cell lung cancer (n=2)	27.00 ± 9.89

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*p < 0.001

Table-5: Area under the Receiver Operating Characteristic (ROC) Curve

Test Result Variable	Area	Std. Error	p-value	95% confidence Interval (CI)	
				Lower Bound	Upper Bound
CA-125	0.924	0.025	<0.001	0.875	0.973

Discussion:

The mean age ± SD of the study population is 71.76 ± 8.70 years. The prevalence of disease shows a rising trend with age and is more prevalent in the age group of above 70 years of age. This group wise distribution of lung cancer patients in the present study is comparable with the findings of Yang ZM et al[6] and Tomita M et al[7] who reported the occurrence of lung cancer more in those who are above 65 years of age. In this study, majority of the cases had family history of lung cancer. Nitadori J et al[8] observed in their study that those with a family history of lung cancer were more likely to acquire lung cancer themselves. In this study, majority of the cases are current smokers (42%), followed by ex-smokers (40%) and non-smokers (18%). Doll R and Peto R[9] reported that tobacco smoking is well established as the major aetiological risk factor for lung cancer, contributing to a 10-fold increase in risk in long-term smokers compared with non-smokers.In our study, the level of CA-125 was significantly higher in lung cancer patients (43.17±20.49 U/ml) as compared to control. This finding was consistent with Abbas M et al[10], Diez M et al[11] and Picardo AL et al[12]. In our study it was found that serum CA-125 level increased significantly with stages of lung cancer($p<0.001$), which was in agreement with findings of Diez M et al[11] which showed a significant correlation between increasing serum CA-125 levels and TNM stage in lung cancer patients ($p < 0.01$). In our study, we found significantly higher serum CA-125 level in adenocarcinoma (54.71±10.07 U/ml) which is comparable to the findings of Molina R et al[13], Cedres S et al[14] and Li X et al[15]. In a study conducted by Isaksson S et al[16], CA-125 was significantly associated with recurrent disease in lung adenocarcinoma patients. In the present study, the cut off values for maximum sensitivity for CA-125 in serum was < 27.15 U/ml with 80% sensitivity and 90% specificity.

Conclusions:

Our study may be helpful as assay of the tumour marker is simple and will complement other diagnostic tests of lung cancer. It is, therefore, concluded that the serum CA-125 level might be a valuable biochemical index in the diagnosis of lung cancer. This may be useful in patients in whom tumour cannot be visualized by bronchofibroscopy or to rule out false positive cases. And more importantly, apart from diagnosis, the tumour marker reflects the extent (stage) of the disease at diagnosis and can be useful in predicting how the disease will respond to treatment.

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