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DR-70: A PROMISING BIOMARKER FOR THE DETECTION OF LUNG CANCER

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Abstract – *Objective:* *Lung cancer (LC) is characterized by an aggressive phenotype with a high mortality rate, early metastasis, and proliferation rate. Treatment options and prognosis differ significantly at each stage. Despite the availability of multiple imaging studies and invasive procedures, the disorder is diagnosed at an advanced stage. Therefore, it is essential to find biomarkers for the early detection of LC.*

Patients and Methods: *Between 2018 and 2020, 73 LC and 71 control with the same demographic characteristics were included in our study. DR-70 level was measured by a photometric method in serum samples taken from all subjects.*

Results: *A total of 144 subjects (110 male, 34 female) was included in the study. DR-70 levels in the LC group (2.53±2.64 μg/mL) were found to be statistically significantly higher than the control group (0.56±1.23 μg/mL). Clinical sensitivity and specificity of DR-70 for LC were found to be 87.67% and 88.73%.*

Conclusions: *The high sensitivity and specificity of DR-70 can be used as a biomarker for rapid diagnosis in patients with LC. Compared with other tumor biomarkers, DR-70 seems to have a better sensitivity and specificity in the diagnosis of LC.*

KEYWORDS: *Lung cancer, DR-70, Biomarker, Tumor marker, Early diagnosis.*

INTRODUCTION

Lung cancer (LC) has been the leading cause of cancer death worldwide[1]. After five years, only about 18% of all lung cancer patients are still alive[2]. There are two main types of lung cancer, namely non-small cell lung cancer (NSLC) and small cell lung cancer (SCLC)[3].

The most common class of lung cancer is NSLC, accounting for approximately 85% of

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lung cancer[4], generally subcategorized into adenocarcinoma, squamous cell carcinoma (SqCC), and large cell carcinoma[2]. Smoking is the major cause of the etiology of lung cancers, including the NSLC subtype[5].

Many LC patients currently have an advanced cancer diagnosis, but diagnostic stages may change as lung cancer screening tests become more common[6]. Diagnosing cancer as early as possible is of great importance for the benefit of treatment. Tissue and/or blood biomarkers have been guiding the treatment decision in treating patients with advanced LC. Several diagnostic biomarkers for LC have been developed[5]. Current biomarker tests for patients with LC are Programmed Death-Ligand 1 (PD-L1), Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), Receptor Tyrosine Kinase (ROS1), BRAF (v-RAF murine sarcoma viral oncogene homolog B1), RET (Ret Proto-Oncogene), MET Exon 14 Skipping Mutation (METex14mut), Human Epidermal growth factor Receptor 2 (HER2), KRAS (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog), and Neurotrophic Tyrosine Receptor Kinase (NTRK)[7].

The exogenous coagulation and fibrinolysis activation is a critical factor for tumor growth, invasion and metastasis. For this reason, the production of thrombin, which is the coagulation factor, and the formation of fibrinolysis, are essential for the spread of the tumor. Tumor cells release plasminogen activators that directly activate the fibrinolytic system and plasminogen activators affect the production of fibrin-fibrinogen degradation products (FDPs) in cancer cells[8]. DR-70 is an immunoassay marker that measures both fibrin and FDPs in human serum samples. Many studies have evaluated the clinical performance of DR-70 in the detection of various tumors, including colorectal, tongue, and gastrointestinal cancers[9-16]. These studies indicate that measuring serum DR-70 can be useful for tumor detection.

This study aimed at evaluating the DR-70 immunoassay as a detection biomarker for the presence of lung cancer.

PATIENTS AND METHODS

The study included the same demographic features of newly diagnosed LC patients as well as a stable control group between the dates of 2018 and 2020 in the University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital and University of Health Sciences Turkey, Bagcilar Health Application and Research Center Chest Diseases. The study's Ethics Committee approval was taken from Istanbul Medipol University Non-Invasive Ethics Committee, released decision number 46 on January 3, 2018. Before being included in this study, both patients and the control who were not previously involved signed an informed consent document. To achieve 80% power at a significance level of 0.05, the power analysis needed at least 70 participants for each group. The cancer group was evaluated according to smoking status, staging, and gender. Histopathological examinations for all cases confirmed the lung cancer diagnosis. In the staging of the disease, the TNM 8 lung cancer staging system was used for Stage 1-2 as the early stage of the disease and Stage 3-4 for the advanced stage of the disease[17]. Nine mL of blood was taken from each participant into the biochemistry tube, and after clotting, the blood was centrifuged at 3000 rpm for 10 minutes and stored at -80°C until the study was completed. Serum DR-70 level was measured by the photometric method with commercially purchased ELISA kits (Elabscience) in all participants.

STATISTICAL ANALYSIS

IBM SPSS 25.0 package program (SPSS Inc., Armonk, NY, USA) was used for statistical analysis. Frequency and percentage values were presented for qualitative variables. Arithmetic mean ± standard deviation, median, minimum and maximum values were presented for quantitative variables. A Chi-square test was used for comparisons between two qualitative variables. An independent sample *t*-test was used for comparisons between qualitative variable categories in terms of quantitative variables. ROC (receiver operation curve) analysis was performed to examine the use of DR-70 values in diagnosing malignancy. The variables found to be significant due to paired comparisons were included in the model, and logistic regression analysis was applied. Type I error rate was taken as 0.05 in the study.

RESULTS

Between 2018 and 2020, the study involved 144 participants, 49.3% (n=71) of whom were control, and 50.7% (n=73) of whom were malignancy, 76.4% (n=110) of whom were male, and 23.6% (n=34) of whom were female, at Health Science University Turkey Yedikule Education and Research Hospital and University of Health Sciences Turkey Bagcilar Health Application and Research Center Chest Diseases in Istanbul. Table 1 reveals that 19.4% (n=28) of study participants were nonsmokers, while 80.6% (n=116) were smokers.

TABLE 1. Characteristics of the participant.

	N (%)
Group	
Control	71 (%49.3)
Malignant	73 (%50.7)
Gender	
Male	110 (%76.4)
Female	34 (%23.6)
Cigarette	
Not smoking	28 (%19.4)
Smoking	116 (%80.6)

The participants in the study were on average 59.63±9.74 years old, smoked 35.38±27.98 pack-years, and had DR-70 levels of 1.56±2.29 (Table 2).

TABLE 2. General age, cigarette, and DR-70 levels.

	x±SD	*Med (min-max)*
Age	59.63±9.74	59 (44-82)
Cigarette box/Year	35.38±27.98	30 (0-120)
DR-70	1.56±2.29	0.54 (0.17-10)

ROC research was used to determine the usability of the DR-70 marker as a diagnostic instrument, and the AUC (Area Under the Curve) value was found to be 0.921 (p <0.001). The sensitivity was 87.67, and the specificity was 88.73 for the specified cut-off point (> 0.53) (Table 3).

The chi-square and independent samples t-tests were used to measure the qualitative (cigarette and gender) and quantitative (age and number of cigarettes smoked) effects of malignancy (Table 4 and 5).

Binary logistic regression analysis was applied to determine the factors affecting malignancy conditions. As a result of the study, it has been determined that a 1-unit increase in cigarette box-year value is a 1.029-fold risk factor in terms of malignancy. Also, the DR-70 value is more significant than 0.53 is a 42.865-fold risk factor in malignancy conditions (Table 6).

The relationship between DR-70 levels and NSLSC status and malignancy was examined and presented in Table 7.

TABLE 3. DR-70 diagnostic test results.

	Sensitivity	*Specificity*	*AUC (95% CI)*	*Cut-off*	p
DR-70	87.67	88.73	0.921 (0.865-0.960)	>0.53	<0.001*

TABLE 4. Comparison of malignancy conditions and qualitative variables.

	Control (%)	*LC (%)*	*Total (%)*	*Chi-square*	p
Not smoking	22 (78.6)	6 (21.4)	28 (100)	10.501	0.001*
Smoking	49 (42.2)	6 (21.4)	28 (100)	10.501	0.001*
Male	44 (40)	66 (60)	110 (100)	14.602	<0.001*
Woman	27 (79.4)	7 (20.6)	34 (100)	14.602	<0.001*

TABLE 5. Comparison of quantitative variables in terms of malignancy conditions.

	Control	*LC*	*Chi-square*	p
Age	54.85±7.19	64.29±9.67	-6.661	<0.001*
Cigarette box/Year	22.34±21.59	48.05±27.76	-6.194	<0.001*

TABLE 6. Determination of factors affecting malignancy conditions.

	S.E.	*Wald*	*Sig.*	*OR (95% CI)*
Gender (ref: male)	0.812	1.963	0.161	0.32 (0.065-1.575)
Age	0.032	3.312	0.069	1.061 (0.995-1.13)
Cigarette Pack year	0.014	4.437	0.035*	1.029 (1.002-1.057)
Binary DR-70 (ref: ≤0.53)	0.609	38.054	<0.001*	42.865 (12.988-141.471)
Constant	1.947	5.945	0.015*	0.009

TABLE 7. The relationship between stage and malignancy with DR-70 (µg/mL).

Stage	*N*	*x±SD*	*MED (MIN-MAX)*
Stage I	5	0.73±0.36	**0.69 (0.28-1.19)**
Stage II	4	2.84±4.78	0.495 (0.35-10)
Stage III	27	1.75±1.44	**1.64 (0.37-6.47)**
Stage IV	37	3.31±3.01	**2.7 (0.45-10)**
Malignant general	**73**	**2.53±2.64**	**1.69 (0.28-10)**

DISCUSSION

The DR-70 immunoassay marker measures fibrin and fibrin degradation products in human serum. DR-70, which is described as Initial Plasmin Degradation Product (IPDP), which is FDP (fibrin/fibrinogen degradation product) is produced in excess by proteolytic enzymes secreted from cancer cells. A clear association between increased FDP and IPDP levels and cancer detection has been demonstrated[18].

Therefore, FDP, IPDP measurement is used in some cases of malignant tumors. DR-70 analysis has previously been shown to be effective in detecting malignancy in tissues such as the nasopharynx, gastrointestinal tract, breast, ovary, and prostate[19,20].

This study aimed at evaluating the DR-70 immunoassay as a detection biomarker for the presence of lung cancer.

An ideal tumor marker should theoretically be highly sensitive and highly specific to avoid false positive results and have 100% accuracy in healthy individuals and patients with tumor[21]. For a marker to be advantageous for cancer, it must begin to rise before neoplastic process[22].

In this research, we found the percentage of the specificity and sensitivity of DR-70 in LC patients were higher. Our results were similar in a clinical trial by Arinc et al[9]; the clinical specificity and sensitivity of serum DR-70 concentration for Non-Small-Cell Lung Carcinoma (NSCLC), respectively. Wu et al[18] found that the clinical specificity and sensitivity of serum DR-70 concentration for lung cancer patients were 95% and 87%. A clinical trial carried out by Motamed-Khorasani et al[23] have found that the clinical specificity and sensitivity of serum DR-70 concentration for NSCLC were 87.5% and 65.2%, respectively. In our study, sensitivity and specificity of serum DR-70 concentration for LC were 87.67% and 88.73%, respectively. The specificity and sensitivity of serum DR-70 concentration results of our study were similar to previous studies. However, our study's sensitivity of serum DR-70 concentration results was higher than Arinc et al[9] and Motamed-Khorasani et al[23] studies. A clinical trial by Arinc et al[9] have found that the serum concentration of DR-70 for NSCLC tumor type was higher in the lung cancer group than in the control group. In our study, the LC group of patients had a higher serum DR-70 than the control group. The serum DR-70 concentration of our research has similar results to Arinc et al[9] study. Our results of mean value and SD of DR-70 in general malignant cases were different from Sengupta et al[24] study. This difference may be due to the difference in the distribution of malignancy stages in the Sengupta et al[24] study. The study's limitation is that it only included a limited number of patients and staging.

CONCLUSIONS

DR-70, which has high sensitivity and specificity, may be a biomarker for lung cancer diagnosis with a high mortality rate. Further studies with the DR-70 are needed to elucidate LC disease processes and increase the speed of diagnosis.

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Ethical Approval:

The study's Ethics Committee approval was taken from Istanbul Medipol University Non-Invasive Ethics Committee, released decision number 46 on January 3, 2018.

Informed Consent:

Before being included in this study, both patients and the control signed an informed consent document.

Conflict of interest:

The Authors declare no conflict of interest.

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