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Pre-Treatment Diagnostic and Predictive Value of Programmed Cell Death-Ligand 1, Matrix Metalloproteinase-9, and Cytokeratin 19 Fragment Antigen 21.1 Markers in Primary Lung Cancer

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ABSTRACT

Background and Objective: The precise role of immunological tumor markers in diagnosing lung cancer remains unclear, although there has been significant research. This study aims to investigate the diagnostic and predictive value of pre-treatment programmed cell death-ligand 1 (PD-L1), matrix metalloproteinase-9 (MMP-9), and cytokeratin 19 fragment antigen 21.1 (CYFRA21-1), and Tumor necrosis factor (TNF-α), and Interleukin 6 (IL-6) in primary lung cancer.

Methods: This cross-sectional study was conducted on 75 patients with lung cancer, aged 40 to 75 years. The patients were selected from among those who had not started any treatment (chemotherapy, radiotherapy, etc.) and did not have any other type of cancer. These patients were divided into two groups: 23 patients with small cell lung cancer (SCLC) and 52 patients with non-small cell lung cancer (NSCLC). 60 controls were selected from among the participants who were in excellent health and were between 40 and 70 years old. PD-L1, MMP-9, CYFRA21-1, IL-6 and TNF-α were evaluated in the patients and the control group using ELISA.

Findings: The results show that the PD-L1 and MMP-9 levels were significantly higher in NSCLC (9.67±0.12 and 8.64±0.28ng/ml, respectively) and SCLC groups (9.26±0.12 and 7.88±0.56 ng/ml respectively), compared to the healthy group (4.84±0.07 and 0.26±0.19 ng/ml, respectively) ($P \leq 0.01$). Similarly, CYFRA21-1 levels were significantly higher in both the NSCLC (3.46±0.11 ng/ml) and SCLC (3.70±0.15 ng/ml) compared to the healthy group (1.92±0.10 ng/ml), also with $P \leq 0.01$. Additionally, TNF-α and IL-6 levels were significantly higher in both NSCLC and SCLC groups compared to the healthy group.

Conclusion: The results of the study showed that the levels of PD-L1, MMP-9, CYFRA21-1, TNF-α, and IL-6 are significantly increased in patients with lung cancer, and these biomarkers can probably be used to predict lung cancer and its clinical stages.

Keywords: *Small Cell Lung Cancer, Matrix Metalloproteinase-9, Lung Cancer, TNF-α.*

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Introduction

Lung cancer is a malignant tumor that develops in lung tissues and is one of the worst cancers worldwide, causing death in both men and women (1). Roughly two million people are affected by lung cancer each year; most cases are discovered in their advanced stages (2). Lung cancer is generally divided into two primary categories: non-small cell lung cancer and small cell lung cancer (3).

In Iraq, lung cancer has been a matter of concern and a growing issue due to several factors, including smoking habits, exposure to environmental pollutants, and changes in lifestyle and diet (4). Although the diagnosis of lung cancer has improved due to advancements in imaging methods, the majority of cases of lung cancer appear at late stages of the disease, at which point their therapy options are restricted. Early diagnosis of lung cancer is crucial (5). Measurement of immune tumor markers is a benefit for the early clinical diagnosis of lung cancer (6). Tumor markers can serve as an additional tool alongside clinical and other diagnostic tests to detect cancer development and track treatment effectiveness (7). Current immune tumor markers in serum include Programmed cell death 1 ligand 1, matrix metalloproteinase-9, Cytokeratin 19 fragment antigen 21.1, tumor necrosis factor-alph and interleukine-6.

PD-L1 is an immune regulator that induces immunosuppression by interacting with programmed death-1 (PD1) receptors on T cells (8). It regulates T cell functions by having a negative costimulatory effect, which hinders the release of cytokines, speeds up the death of activated T cells, and stimulates T-cell (9). In lung cancer, PD-L1 expression is significant because it can be targeted by immunotherapy drugs known as immune checkpoint inhibitors, which have been developed and successfully used in the treatment of various types of cancer (8, 9). Many cancer cells express PD-L1 on their surface, cancer cells can engage PD-1 receptors on T cells, consequently suppressing antitumor immune response. This interaction leads to T cell exhaustion and reduced tumor cell death, allowing cancer cells to proliferate and spread (10, 11).

Similarly, CYFRA21-1 seems promising in diagnosing lung cancer and monitoring treatment effectiveness (12). CYFRA21-1 is a tumor biomarker that has been identified relatively recently and could be helpful in differentiating between malignant and benign lung illnesses, such as those exhibiting nodular shadows on imaging scans (6, 7, 13). It works based on the regulation of multiple processes, including the survival of cancer cells, migration, immune response stimulation, and the creation of the cancer microenvironment (14, 15). Researchers studying cancer find MMP-9 to be a highly intriguing and potentially useful tumor marker with good sensitivity and specificity for NSCLC (15). In light of this, the current study aims to investigate the diagnostic and predictive value of pre-treatment PD-L1, MMP-9, CYFRA21.1, TNF-α, and IL-6 in primary lung cancer.

Methods

In this cross-sectional study, 75 lung cancer patients, in the age range of 40-73 years were collected at the Anbar Cancer Center and the Cancer Center in Baghdad Teaching Hospital, Medical City. The collection of specimens began in December 2022 and continued through the end of November 2023. Of these patients, 52 had NSCLC (32 were men and 20 were women), and 23 had SCLC (15 males and 8 females). The oncologist made the diagnosis according to the outcomes of physical exams, biopsy, radiology, and bronchoscopy. In order to provide a comparison, the study included 60 samples as a control group (32 males and 28 females), in the age range of 40 to 70 years.

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The Research Ethics Committee at the University of Anbar/College of Medicine approved the study protocol with ethical Code 123 on November 23, 2023. In addition, approval code 2022082 was obtained from the Research Committee in the Ministry of Iraqi Health and Environment.

Sample selection: Patients were included if they had recently been diagnosed with lung cancer and had not started any treatment (chemotherapy, radiotherapy, etc.). Exclusion criteria included those initiating therapeutic approaches, those with chronic diseases, or those with other types of cancer. The controls were selected at the time of sampling from among participants who were in excellent health, and did not have acute infections, impaired immune systems, hypertension, diabetes, or any other endocrine problems.

Data collection and laboratory measurements: Prior to collecting blood, every patient and control had a thorough medical history obtained via interview, which included sex, age, height, weight, duration of lung cancer, and smoking, and prior to taking part in this study, each participant gave written informed consent. Each participant had 5 ml of blood drawn using a disposable syringe after fasting for 12 hours. To obtain sera, the blood samples were kept in white tubes, left to coagulate for 30 minutes, and then subjected to centrifugation at 5000 rounds per minute, and then sera were moved into Eppendorf tubes, where they were kept at -80°C until the analysis. The laboratory employed the ELISA to evaluate the samples using kits for Human PDL1 (Cat. No: ELK3055), Human CYFRA21-1 (Cat. No: ELK1967), Human MMP-9 (Cat. No: ELK1262), Human Interleukin-6 (Cat. No: ELK1156), and TNF-α. All ELISA kits were supplied by ELK biotechnology company, China. The tumor indicators were examined according to the procedures suggested by the manufacturer of the kit, and the color of the samples was measured using ELISA reader at a wavelength of 450±10 nm. The levels of these markers in the samples were determined by comparing their optical density (OD) to a standard curve.

The effect of variance variables on the study biomarkers was established using the SAS (2018) program. To statistically compare means, T-test and ANOVA with LSD (least significant difference) test were utilized. The chi-square test was used to statistically evaluate the various kinds of lung cancer. The estimation of the correlation coefficient between the variables was done in the research ($p \leq 0.01$). Determining the study parameters' diagnostic specificity and sensitivity was done using the ROC curve. To evaluate serum parameters' capacity to distinguish between lung cancer patients and controls with precision, the area under the curve was calculated. The optimal diagnostic cut-off value for achieving the highest clinical specificity and sensitivity was identified through ROC curve analysis.

Results

Clinical characteristics of the Study Groups: The mean age of patients was 65.25±0.82 years, while the control group was 64.14±1.23 years. The control group's BMI was 25.52±0.68 kg/m2, and the lung cancer patients' mean BMI was 24.30±0.33 kg/m2. Patients with lung cancer were more likely to be smokers (72%) than non-smokers (28%), p=0.0001. When compared to non-smokers (63.3%), the control group had a higher percentage of smokers (36.6%), p=0.0092. However, in the groups of lung cancer patients and control, the percentage of males was higher than the percentage of females, $p \leq 0.01$. According to the current study, patients with NSCLC had a significantly larger percentage (69.3%) than patients with SCLC (30.6%) at $p \leq 0.01$. In addition, the TNM, or staging method, which is according to the outcomes of physical examinations and other tests, divides the patients in this study into four stages. A large proportion of patients (37.3%) are in the IV stage, followed by the III stage (28%), while stages I and II (14.6% and 20%), respectively, have lower percentages at $p \leq 0.01$ (Table 1).

Determination of immunological parameters between difference groups: At the $p \leq 0.01$ level, there was a significant increase in the PD-L1 levels in the NSCLC and SCLC groups (9.67±0.12 and 9.26±0.12),

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respectively, when compared to the control group (4.84±0.07). MM-9 levels showed a significant rise in both the NSCLC and SCLC (8.64±0.28 and 7.88±0.56), respectively, compared to control groups (4.26±0.19) at p≤0.01. CYFRA21-1 level showed a significant increase in SCLC and NSCLC (3.70±0.15 and 3.46±0.11), respectively, compared to the control group (1.92±0.10). The findings show that there was a significant increase in TNF-α levels in SCLC and NSCLC (59.72±1.89 and 55.87±1.84, respectively), as compared to the control group, which had a level of 28.90±0.71, at p≤0.01. However, as compared to other groups, the SCLC group had a significant rise in IL-6 (54.46±2.11) ng/ml (p≤0.01) (table 2).

Table 1. The clinical features of lung cancer patients and the healthy control

Clinical Characteristics	Lung cancer group (n=75)	Control group (n=60)	t-test	p-value
Age in year, Mean±SE	65.25±0.82	64.14±1.23	3.125	0.056^{NS}
BMI, Mean±SE	24.30±0.33	25.52±0.68	1.334	0.082^{NS}
Sex, Number(%)				
Male	47(62.6)	32(53.3)	-	0.0011^{**}
Female	28(37.4)	28(46.6)		0.063^{Ns}
Smoking, Number(%)				
Smoker	54(72)	22(36.6)	-	0.0001^{**}
No smoker)	21(28)	38(63.3)		0.0092^{**}
Lung cancer type, Number(%)				
SCLC	23(30.6)	-	-	0.0013^{**}
NSCLC	52(69.3)			
Stages, Number(%)				
I	11(14.6)	-	-	0.041^{*}
II	15(20)			
III	21(28)			
IV	28(37.3)			

BMI= Body Mass Index, NS: Non-Significant

Table 2. Comparison between study groups in PD-L1, MM-9, CYFRA, TNF-α, IL-6

Parameter	NSCLC Mean±SE	SCLC Mean±SE	Control Mean±SE	LSD value	p-value
PD-L1 (ng/ml)	$9.67±0.12^{a}$	$9.26±0.12^{a}$	$4.84±0.07^{b}$	0.354^{**}	0.0001
MM-9 (ng/ml)	$8.64±0.28^{a}$	$7.88±0.56^{a}$	$4.26±0.19^{b}$	0.996^{**}	0.0001
CYFRA (ng/ml)	$3.46±0.11^{a}$	$3.70±0.15^{a}$	$1.92±0.10^{b}$	0.348^{**}	0.0001
TNF-α (ng/ml)	$55.87±1.84^{a}$	$59.72±1.89^{a}$	$28.90±0.71^{b}$	5.066^{**}	0.0001
IL-6 (ng/ml)	$46.17±1.18^{b}$	$54.46±2.11^{a}$	$26.40±1.01^{c}$	4.088^{**}	0.0001

Distinct letters in the same column mean significant difference. **(p≤0.01).

Immunological tumor marker levels in lung cancer according to lung cancer stages: At Stage IV, all immunity parameters showed a significant increase compared to the other stages. Specifically, mean PD-L1 at Stage IV (10.06±0.13) displayed a significant rise in comparison to the other stages, but there was no significant variation between Stages III and II compared to Stage I (8.21±0.23) p≤0.01. Meanwhile, the mean MMP-9 levels showed no significant difference between Stage IV and Stage III compared to Stages II and I. Regarding CYFRA21.1, there was a significant decrease in Stage I (2.89±0.22) in contrast to the

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other stages (p≤0.01). IL-6 and TNF-α exhibited a significant increase at Stage IV (55.29±1.51 and 60.37±1.98), respectively, in contrast to the other stages at p≤0.01. Mean IL-6 and mean TNF-α, however, did not alter much between Stages I, II, and III (table 3).

Correlation coefficient between parameters in study groups: The results show positive and significant correlations between PD-L1 with MM-9 (r=0.55, p=0.0001; figure 1.A) in lung cancer patients. There were no significant correlations between PD-L1 with CYFRA21.1 (r=-0.10, p=0.415), PD-L1 with TNF-α (r=-0.13, p=-0.305), and PD-L1 with IL-6 (r=-0.08, p=-0.540) in lung cancer patients. All correlations in the control were non-significant. The positive correlations imply that PD-L1 and MMP-9 levels in lung cancer patients are likely to rise (Table 4).

Table 3. Effect of stage in immunity parameters of lung cancer patient group

Stage	Mean±SE				
	CD274 (ng/ml)	MMP-9 (ng/ml)	CYFRA 21.1 (pg/ml)	IL-6 (ng/ml)	TNF-α (ng/ml)
I	8.21±0.23^{c}	8.31±0.68^{c}	2.89±0.22^{c}	47.04±2.67^{b}	51.90±2.27^{b}
II	8.85±0.17^{b}	8.86±0.60^{bc}	3.46±0.20^{b}	48.58±1.91^{b}	52.68±1.37^{b}
III	9.33±0.22^{b}	9.81±0.45^{ab}	3.95±0.16^{a}	50.39±2.32^{ab}	57.61±2.93^{ab}
IV	10.06±0.13^{a}	10.46±0.22^{a}	4.36±0.09^{a}	55.29±1.51^{a}	60.37±1.98^{a}
LSD value	0.560**	1.280**	0.469**	6.231*	7.335*
p-value	0.0001	0.0026	0.0001	0.020	0.0359

Distinct letters in the same column mean significant difference. **(p≤0.01).

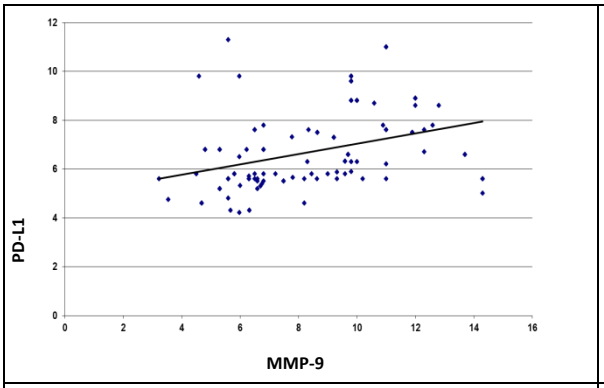


Figure (1-A). The relationship between PD-L1 and MMP-9 in Lung cancer patients

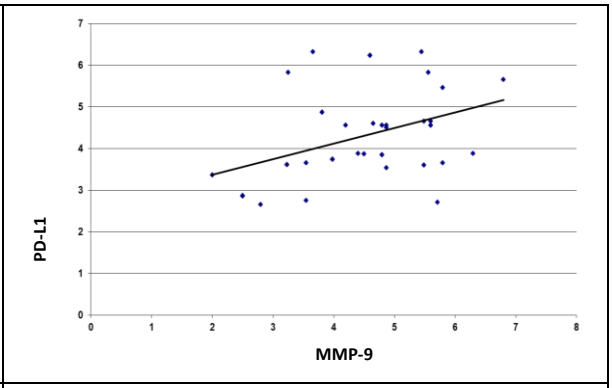


Figure (1-B). The relationship between PD-L1 and MMP-9 in control

Table 4. Correlation coefficient between studied markers in lung cancer and controls

Parameters	Correlation coefficient-r			
	Patients group		Control group	
	Correlation coefficient-r	p-value	Correlation coefficient-r	p-value
PD-L1 and MMP-9	0.55**	0.0001	0.30^{NS}	0.081
PD-L1 and CYFRA21.1	-0.10^{NS}	0.415	0.20^{NS}	0.245
PD-L1and TNF-α	-0.13^{NS}	0.305	-0.02^{NS}	0.894
PD-L1 and IL-6	-0.08^{NS}	0.540	-0.24^{NS}	0.168

**(p≤0.01), *(p≤0.05), NS: Non-Significant.

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Determination of the study parameters' diagnostic sensitivity and specificity within study groups: The ROC analysis of PD-L1, MMP-9, CYFRA21.1, TNF-α, and IL-6 concentrations in lung cancer patients and control. PD-L1 concentration greater than 6.55 ng/ml demonstrated a sensitivity 100% and specificity 98% for lung cancer diagnosis. MMP-9 concentration greater than 5.89ng/ml demonstrated a sensitivity 95% and specificity 81% for lung cancer diagnosis. CYFRA21.1 concentration greater than 2.81ng/ml demonstrated a sensitivity of 95% and specificity of 75% for lung cancer diagnosis. TNF-α and IL-6 concentrations greater than (35.18 and 36.16) ng/ml demonstrated a sensitivity of (99% and 95%, respectively) and specificity of (94% and 94%, respectively) for lung cancer diagnosis, as shown in Table 5 and Figure 2.

Table 5. Sensitivity, specificity, PPV, NPV, accuracy for study parameters in lung cancer

Parameter	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
PD-L1	6.55 ng/ml	100%	98%	98%	95.1%	97.6%
MMP-9	5.89 ng/ml	95%	81%	95.4%	88.2%	85%
CYFRA21.1	2.81 ng/ml	95%	75%	93%	61.3%	87.6%
TNF-α	35.18 ng/ml	99%	94%	98.5%	88.6%	95.5%
IL-6	36.16 ng/ml	95%	94%	95.2%	88.2%	95%

*PPV= positive predictive value, NPV= Negative predictive value

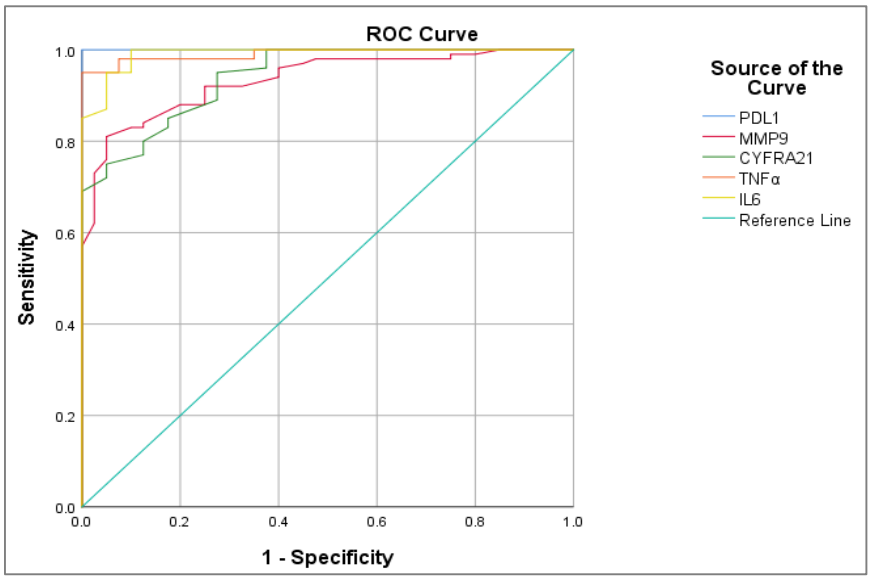


Figure 2. ROC curve analysis for PD-L1, MMP-9, CYFRA21.1, TNF-α, and IL-6 concentrations (Lung cancer patients and controls). PD-L1 ROC AUC= 1.000; 95% CI, 1.000-1.000. MMP-9 ROC AUC= 0.934; 95% CI, 0.895-0.973. CYFRA21.1 ROC AUC= 0.940; 95% CI, 0.904-0.977. TNF-α ROC AUC= 0.991; 95% CI, 0.980-1.000. IL-6 ROC AUC= 0.991; 95% CI, 0.979-1.000. The sensitivity and specificity of lung cancer diagnoses were more than 75%.

Discussion

In this study, we found that PD-L1, MMP-9, CYFRA 21.1, TNF-a, and IL-6 levels increased in Iraqi lung cancer patients in contrast to control group. Our results are similar to results by (16-18), who indicated that PD-L1 increased in lung cancer in contrast to control. A previous study indicated that high PDL-1 was associated with poor prognosis (19). According to one study, elevated PD-L1 could represent an additional

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mechanism during neoplastic transition that offers a targeted path for immune evasion; as a result, these tumors may be especially susceptible to immune checkpoint inhibition (20). A great deal of work has gone into creating predictive biomarkers, such as MMP-9 (21), CYFRA 21-1 (22), and PD-L1 value (23), with the goal of identifying patients who would benefit from PD-1/PD-L1 immunotherapy. Few studies have examined the connection between PD-L1 level and the clinical findings of cancer patients, despite some prior research showing that high PD-L1 levels is linked to a bad prognosis in patients with various forms of cancer (24, 25). These results suggest that PD-L1 may influence tumor immunity and maintain immunological homeostasis. It has been found that sex, age, smoking, and histological type history do not significantly affect the PD-L1 level in the serum of lung cancer patients (26). Similarly, in the current investigation, the PD-L1 concentration varied according to lung cancer stage but was unaffected by patient factors, including sex and smoking history (25).

The results of Pastor et al. (27) are in agreement with us in finding no differences between the various histological types (NSCLC and SCLC) of lung cancer and levels of CYFRA 21-1. Prior to treatment, lung cancer patients' levels of tumor markers have often been greater than those of control groups. A previous study indicated that the levels of CYFRA 21-1 were significantly higher in patients with lung cancer compared to those with benign lung diseases. They came to the conclusion that, when combined with additional clinical and radiographic data, CYFRA 21-1 may be successfully used in the differential diagnosis between benign and malignant lung illnesses (28). Our results agree with earlier research by Jumper et al. (29), Zhang et al. (30), and El-Badrawy et al. (31) who indicate that MMP-9 is elevated in the lung cancer patients' serum when compared to the controls. Consistent with the results of Duda et al. (32), our results showed that the MMP-9 levels were significantly greater in the cancer group. However, our results were not consistent with some other findings (32), which reported that no significant relationship was seen between several clinical parameters (tumor histology, stage, or nodal status) and plasma MMP-9 levels. MMP-9 has been found to have a significant role in the growth of lung cancer, as evidenced by its significantly increased activity and expression in tumor tissue compared to surrounding tissue (31).

According to data by Zhang et al. (30), advanced lung cancer appears to change the typical MMP-9 circulatory pattern. This may facilitate the invasion and/or spread of the tumor. A worse prognosis was linked to high tumor cell expression of MMP-9, indicating the necessity for MMP inhibitor research as a cancer treatment and possibly predictive data. According to a short study (29), MMP-9 levels were approximately doubled for MMP-9, but they were 3.6 times higher in cancer patients than in controls. They did not, however, speculate as to where the MMP-9 originated and instead did not believe that the significant rise was a result of the tumor cells producing too much of the protein. We believe that maybe, as Kwaan et al (33) has proposed, the extracellular matrix (ECM) MMPs are being activated by circulating urokinase plasminogen activator (uPA), which leads to MMP-9 releasing into the bloodstream during this ECM breakdown process (29, 30). In lung cancer, MMP-9 expression may be a major predictive factor for both survival and mortality (34). Given that there was no significant difference in MMP-9 between NSCLC and SCLC, despite the fact that both had values much higher than normal, this shows that the pathological alterations in the tumor with regard to MMP-9 are equally reflected in both tumors (29).

According to this study, lung cancer was associated with elevated levels of TNF-α and IL-6. Our findings concur with findings by Nicola et al. (35) and Kalali et al. (36) who found that IL-6 increased in lung cancer contrast to control group. Compared to alveolar macrophages of nonmalignant lung cancer patients, those with lung cancer patients released considerably more cytokines IL-6, and TNF-α (37). Important polypeptide mediators in the immunological response are cytokines, including TNF-α, IL-6 and IL-1 (38). Since sensitivity of target cells to TNF-α increased by inhibitors of these proteins' synthesis, it is confirmed that tumor cells are able to manufacture protein that shields them from TNF-α-induced lysis (36). The

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cooperative activity of cytokines is crucial for efficient tumor defense; TNF-α, IL-1, and IL-6 all boost T-cell responses (36, 38). Similar findings were reported in a study by Essogmo et al. (38) who discovered that individuals with SCLC and NSCLC had similar levels of IL-6. According to one study, IL-6 is known as a high-sensitivity and high-specificity molecular biomarker for lung cancer metastatic identification and survival prediction, regardless of clinical type (24). This could improve the specificity and sensitivity of lung cancer diagnosis. According to a different study, a high level of circulating IL-6 is an independent predictor for survival specific to lung cancer, particularly for those who underwent chemotherapy, and may predict a poor response to chemotherapy (36, 37).

When considering the TNM stage of cancer, the results show a significant correlation between PD-L1, CYFRA 21-1, MMP-9, TNF-α, and IL-6 with the TNM stage, as reported in the literature (27). This explains the correlation between these marker levels and both stage and tumor size, which may reflect the tumor mass (28). According to our findings, patients with late-stage lung cancer had mean tumor marker levels that were higher than those of patients with early-stage lung cancer. Certain tumor marker levels are sensitive to changes in tumor stage and rise in tandem with the advancement of cancer. Since there is a significant increase in PD-L1, MMP-9, CYFRA21-1, TNF-α, and IL-6 levels in lung cancer patients, especially when the disease is in Stage IV, these biomarkers can be used to predict lung cancer and its clinical stages.

Conflict of interests: No conflict of interests was declared by the authors.

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