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Prevalence of programmed cell death ligand 1 (PD-L1) Expression among Tumor Samples from Iraqi Patients with Non-Small Cell Lung Cancer

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Abstract

Background: In a subgroup of patients with advanced stage lung cancer, immunotherapy that specifically targets the PD-L1/PD-1 pathway has been demonstrated to enhance survival. Expression of PD-L1 in cancer cells has been recognized as a promising biomarker for predicting the probable response of patients to anti-PD-L1 or anti-PD-1 therapy. The objective of this study is to examine the frequency of PD-L1 expression in non-small cell lung cancer (NSCLC) in Iraqi patients and its association with clinicopathological parameters that can offer useful insights for making treatment approaches more effective and enhancing clinical outcomes.

Methods: This is a cross sectional study on 94 non-small cell lung cancer tumor samples collected from teaching laboratories of Medical City Teaching Complex. The programmed cell death ligand 1 (PD-L1) expression was evaluated using immunohistochemistry. PD-L1 protein expression level is established by usage of Tumor Proportion Score (TPS). The specimen would be regarded to possess positive PD-L1expression result if the TPS ⩾ 1% and to have high PD-L1 expression if the TPS ⩾ 50%. PD-L1 expression is then compared with different clincopathological features.

Results: Positive PD-L1 expression (⩾1%) was seen in 39 cases (41.5%) of NSCLC patients. In 12 cases (12.7%), there was high expression in ⩾50% of tumor cells. of NSCLCs. A non-significant association was found between age& PD-L1 scores. While PD-L1 levels were significantly expressed with higher levels in female patients than males.

Conclusions: High levels of PD-L1 expression is observed in a significant percentage of NSCLC. Immunohistochemistry is needed to reveal cases that benefit from immunotherapy. A lower patient age was correlated with higher PD-L1 expression.

Introduction

One of the most prevalent cancers in the world and a major contributor to cancer-related mortality is lung cancer with over 1700000 deaths reported to the World Health Organization (WHO) each year. According to the American Cancer Society, lung cancer exceeds the combined mortality rates of prostate, colon, and breast cancers [1]. During the last years in Iraq, the rate of lung cancer increased significantly during the period of 2000–2016 (from 4.08 to 5.60/100 000 ($p = 0.038$)). Males are affected more than females with approximately a ratio of 3:1, and it tends to increase with increasing age [2]. About 80% of all instances of lung cancer are non-small cell lung cancer (NSCLC) [3]. This entity of lung cancer includes many types; most common are the adenocarcinoma (AC) and the squamous cell carcinoma (SCC) [4]. A slight improvement in prognosis of the disease is related to the early diagnosis and the employment of the latest targeted therapies even in patients with advanced stages of the cancer [3].

A novel method of lung cancer therapy is immunotherapy. It also contributes to such prognosis improvements. Targeting the immune checkpoint molecules like PD-1 or PD-L1, monoclonal antibodies have emerged as a significant immunotherapy modality for the treatment of cancer. While immunotherapy has shown significant benefits as both first- and second-line treatments for advanced non-small cell lung cancer (NSCLC), the relation between PD-L1 expression and the clinical outcomes is still an area for active research and debate [5].

The use of monoclonal antibodies that target the interaction between PD-L1 and PD-1, such as pembrolizumab and nivolumab, has greatly increased the survival rate for those suffering from non-small cell lung cancer (NSCLC). These medications serve to activate the immune system and hence improve the body's ability to target cancer cells by inhibiting the PD-L1/PD-1 interaction [6–10]. By inhibiting the kinases involved in T-cell activation, the binding of PD-1 ligands to their receptors, PD-L1 and programmed death ligand-2 (PD-L2), will stop the reaction of the innate cytotoxic T-cell against the malignancy [11–13]. The innate immune system can be stimulated and the body's capacity to identify and combat cancer cells can be increased by immunotherapy employing anti-PD-L1 or anti-PD-1 antibodies. Following the recent regulatory approval of pembrolizumab (anti-PD-1, Merck, Kenilworth) and nivolumab (anti-PD-1, Bristol-Myers Squibb, Lawrenceville, NJ) by the U.S. Food and Drug Administration (FDA), it is critical to identify predictive biomarkers for anti-PD-1/PD-L1 therapy in order to optimize patient selection for treatment while minimizing the risk of adverse effects from the agents targeting that axis [7, 9, 14]. A PD-1 inhibitor called pembrolizumab was licensed by the American (FDA) and European (EMA) drug administrations for use as first-line treatment for non-small cell lung cancer. For NSCLC, patients who express PD-L1 in at least 50% of their tumor cells (TCs) may be candidates for pembrolizumab monotherapy. This implies that tumor tissue samples from these patients should undergo PD-L1 immunohistochemistry testing to ascertain the degree of PD-L1 expression.

The Dako 22C3 pharmDx assay was utilized in the clinical trials for Pembrolizumab (Keytruda) monotherapy in non-small cell lung cancer (NSCLC) to assess the expression levels of PD-L1 in tumor cells [15]. Patients with advanced non-small cell lung cancer (NSCLC) meet the criteria to obtain second-line therapy with pembrolizumab, nivolumab, or atezolizumab. It is recommended to use pembrolizumab in patients with (⩾1%) stained TCs. For all second-line patients, nivolumab and atezolizumab are recommended. Using assays (Ventana SP142 and Dako 28-8 pharmDx), a PD-L1 test is optional. TCs will be measured using Dako 28-8, and cut-offs of ⩾1%, ⩾5%, and ⩾10% will be used. Immune cells (ICs) will score with a cut-off of (⩾10%) stained area, whereas TCs will score with a cut-off of (⩾50%) stained cells in SP142 [16]. Therefore, the purpose of this study is to determine the frequency of non-small-cell lung cancer (NSCLC) in a sample of Iraqi patients having positive expression of programmed cell death ligand 1 (PD-L1), compare the findings with information from clinical trials and international databases, and examine the association between the PD-L1 expression and the various clinicopathological factors.

Methods

This cross-sectional study examined 94 non-small cell lung cancer tumor samples that were gathered between January 2022 and January 2023 from the medical city teaching complex's teaching laboratories.

Sample selection

The inclusion criterion was all histological materials from patients diagnosed with non-small cell lung carcinoma with complete clinicopathological data in a single center within one year period. The exclusion criteria included histological materials with deficient relevant data.

Immunohistochemistry

Programmed cell death ligand 1 expression was evaluated by immunohistochemistry (PD-L1). The Dako 22C3 pharmDx assay, a well-respected and frequently used test for determining PD-L1 expression in NSCLC, was utilized for the testing. Using a monoclonal

antibody against PD-L1 (Clone 22C3), this qualitative immunohistochemistry method finds the PD-L1 protein in FFPE (formalin-fixed and paraffin-embedded) tissue samples from NSCLC patients. The assay is made to work with the Autostainer Link 48 platform's EnVision FLEX visualization system, which enables consistent and repeatable staining. Tumor Proportion Score (TPS), which measures the percentage of live tumor cells that show partial or complete membrane staining of any intensity, is commonly used to evaluate PD-L1 protein expression. The number of PD-L1 positive cells was divided by the total number of viable tumor cells, and then was multiplied by 100 to determine the TPS. As seen in table (1) [17], a TPS of 50% or above is regarded as strong PD-L1 expression, while a TPS of 1% or greater is typically thought to indicate positive PD-L1 expression. Under a light microscope, the stained tissue slices are inspected to assess the staining intensity and compute the Tumor Proportion Score (TPS). Two independent histopathologists evaluate the staining intensity and distribution while doing the estimation at a magnification of ×200. A light microscope was used to estimate the expression of the membrane-bound PD-L1 antigen at a ×200 magnification. Cancer cell cytoplasm staining was disregarded.

Level of expression	TPS	Pattern of staining
No PD-L1 Expression	< 1%	"Partial or complete cell membrane staining (⩾ 1+) seen in < 1% of viable tumor cells"
Low PD-L1 Expression	1–49%	"Partial or complete cell membrane staining (⩾ 1+) seen in ⩾ 1–49% of viable tumor cells"
High PD-L1 Expression	⩾ 50%	"Partial or complete cell membrane staining (⩾ 1+) seen in ⩾ 50% of viable tumor cells"

Table 1: Interpretation of PD-L1 expression according to tumor proportion score. As shown a TPS of 50% or above is regarded as strong PD-L1 expression, while a TPS of 1% or greater is typically thought to indicate positive PD-L1 expression.

Version 24 of SPSS (Statistical Packages for Social Sciences) was used to conduct the statistical analysis. For nominal variables, data were given as percentages and measures of frequency; for quantitative variables, mean and standard deviation were provided. For categorical data, the Pearson Chi-square test and the Fischer Exact test were used to determine the significance of the correlation; for numerical data, the t-test was employed. The null hypothesis is rejected and the results are deemed statistically significant if the computed P-value is equal to or less than 0.05.

Results

The total number of enrolled patients was 94; all of them were diagnosed as cases of (NSCLC). Their mean age (Mean ± S.D.) was 62.01±12.14 years. Number of female patients was 29 (30.85%) while the number of males was 65 (69.14%). Histologically, the most common type was the adenocarcinoma, as shown in table (2:A)

Chi-Square test, along with Fischer Exact test; were used to analyse association among demographics& types of (NSCLC) as shown in table (2:B).Types of NSCLC were non-significantly associated with the age& gender (p-values>0.05).

A. The number and frequency of the histological types of non-small cell lung cancer cases in the study. The most common type was the adenocarcinoma

Histological type	Number of cases (frequency %)
Adenocarcinoma	63 (67.02%)
Other and Unclassifiable carcinoma	14 (14.89%)
Squamous cell carcinoma	13 (13.82%)
Adenosquamous carcinoma	4 (4.25%)

B. The association between age, gender and different types of NSCLC. As shown there is no significant association with the age& gender (p-values>0.05).

Indicators		Types				*P*-value
		Adenocarcinoma N (%)	Squamous N (%)	Adenosquamous N (%)	Unclassifiable N (%)	
Age	⩽60 yrs. No.(49)	35 (37.3)	6 (6.4)	1 (1.1)	7 (7.4)	0.673
	>60 yrs. No.(45)	28 (29.8)	7 (7.4)	3 (3.2)	7 (7.4)	
Gender	Male No.(65)	43 (45.7)	10 (10.6)	3 (3.2)	9 (9.6)	0.929
	Female No.(29)	20 (21.3)	3 (3.2)	1 (1.1)	5 (5.3)	

Table 2: Data interpretation of the studied cases

PD-L1 expression

In our study, positive IHC PD-L1 expression (⩾1%) was observed in 39 cases (41.5%) of NSCLC patients (of them, 27 cases (28.7%) showed PD-L1 TPS (1-49%) and 12 cases (12.7%) showed PD-L1 TPS ⩾50%) while 55 cases (58.5%) showed PD-L1 TPS <1%. A non-significant association was found between age& PD-L1 scores. While PD-L1 levels were significantly expressed with higher levels in female patients than males; (p-value < 0.05) as shown in table (3:A). Regarding PD-L1 expression level in different types of non-small cell lung cancer, the highest PD-L1 levels were in patients with Unclassifiable types, while those with Adenosquamous type; had the minimum levels.

Non-significant relationships were found when comparing among different types according to the Mean PD-L1 levels. The Unclassifiable type was significantly with higher PD-L1 expression than Adenocarcinoma as shown in table (3:B)

Chi-Square test, along with Fischer Exact test; were used to analyse association in table (4:A) which shows that age& gender were non-significantly related to the PD-L1 Expression. Chi-Square test, along with Fischer Exact test; were used to analyse association in table (4:B) which shows a Non-significant relationship between the histological type& the PD-L1 Expression with (p-value>0.05).

*ANNOVA test was used to analyze multiple comparisons.

A. The association between age, gender and PD-L1 tumor proportion score. As shown, there is a non-significant association was found between age& PD-L1 scores. While PD-L1 levels were significantly expressed with higher levels in female patients than males with (p-value < 0.05)

Demographic variables		PD-L1 TPS Mean± S. D.	*P*-value
Age	⩽60 yrs. No.(49)	11.86± 24.06	0.588
	>60 yrs. No.(45)	9.29± 21.58	
Gender	Male No.(65)	8.34± 20.17	0.007
	Female No.(29)	15.76± 27.58	

B. Comparison in PD-L1 expression levels among different types of (NSCLC). As shown, the Unclassifiable type was significantly with higher PD-L1 expression than Adenocarcinoma

Types	PD-L1 TPS Mean± S. D.	Association with other types	*P*-value
Adenocarcinoma No. (63)	7.50± 18.23	Squamous	0.907
		Adenosquamous	0.994
		Unclassifiable	0.044
Squamous No. (13)	12.07± 28.37	Adenocarcinoma	0.907
		Adenosquamous	0.934
		Unclassifiable	0.434
Adenosquamous No. (4)	4.50± 5.25	Adenocarcinoma	0.994
		Squamous	0.934
		Unclassifiable	0.369
Unclassifiable No. (14)	25.06± 33.26	Adenocarcinoma	0.044
		Squamous	0.434
		Adenosquamous	0.369

Table 3: The association between demographic variables, histological types of (NSCLC) and PD-L1 tumor proportion score

A. Association among age, gender & PD-L1 Expression showing that age& gender were non-significantly related to the PD-L1 Expression

Indicators		PD-L1 Expression			*P*-value
		Negative	Positive (Low Expression)	Positive (High Expression)	
		N (%)	N (%)	N (%)	
Age	⩽60 yrs. No.(49)	31 (33)	10 (10.6)	8 (8.5)	0.144
	>60 yrs. No.(45)	24 (25.5)	17 (18.1)	4 (4.3)	
Gender	Male No.(65)	39 (41.5)	20 (21.3)	6 (6.4)	0.294
	Female No.(29)	6 (17)	(7.4)	(6.4)	

B. Comparison among different NSCLC types according to the PD-L1 Expression showing that there is a non-significant relationship between the histological type& the PD-L1 Expression with (p-value>0.05)

Histological type	PD-L1 Expression			*P*-value
	Negative	Positive (Low Expression)	Positive (High Expression)	
	N (%)	N (%)	N (%)	
Adenocarcinoma	39 (41.5)	19 (20.2)	5 (5.3)	0.199
Squamous	9 (9.6)	2 (2.1)	2 (2.1)	0.231
Adenosquamous	1 (1.1)	3 (3.2)	0 (0)	0.194
Unclassifiable	6 (6.4)	3 (3.2)	5 (5.3)	0.178

Table 4: Association between demographics, different NSCLC histological types and PD-L1 Expression.

Table (5) explained that age and PD-L1 were non-significantly& negatively correlated where the increase in age was accompanied by decline in the PD-L1 Expression.

Indicator	Value
Pearson Correlation (*r*)	-0.132
P-value	0.206

Table 5: Correlation between Age& PD-L1.As shown, age and PD-L1 were non-significantly& negatively correlated where the increase in age was accompanied by decline in the PD-L1 Expression

Discussion

Analysing the prevalence of PD-L1 expression in NSCLC patients in Iraq and comparing it to data from other countries can provide valuable information on the regional differences in PD-L1 expression and its potential impact on the use of immunotherapy in NSCLC. Additionally, analysing the relationship between PD-L1 expression and clinicopathological factors such as age, gender and tumor histology can provide insight into the potential predictive value of PD-L1 expression as a biomarker for immunotherapy response. Overall, such a study can provide important information on the prevalence and clinical significance of PD-L1 expression in NSCLC patients in Iraq, and help inform treatment decisions in this patient population.

In this study, lung cancer cases were more common among male patients (69.14%) and this is in agreement with other local and national studies like Al-Rahim et al, Al-Khateeb et al, Pawelczyk et al and Gelatti et al [18-21]. While in past years it was thought to primarily affect males, in recent years the female patients number has risen, so that rates among women are nearly similar to those among men. Sex-based differences in the incidence and diagnosis with respect to lung carcinoma is likely due in part to higher rates of smoking among males, as smoking is a major risk factor for lung cancer. However, there are also other factors that may contribute to the gender difference in lung cancer rates, such as differences in exposure to environmental pollutants or genetic factors. It is important to note, however, that anyone can develop lung cancer, regardless of gender [22].

The mean age of lung cancer patients in our study was 62.01±12.14 years with 52.12% younger than 60 years old and this shows a slightly larger number of young patients than other studies like Pawelczyk et al study in which patients younger than 60 constitute (41.2%) and Al-Khateeb et al study that shows patients in age groups (60-69) and (70-79) years constitutes the majority (64.4%) [19, 20].

Histologically, the most common type of non-small cell lung cancer among our cases was the adenocarcinoma and the least common type was the adenosquamous carcinoma. Adenocarcinoma is the most common type in most recent studies like that of Guarga et al and X. Zhang et al [23, 24], however; in two Iraqi studies, Al-Rahim et al and Al-Khateeb et al, squamous cell carcinoma was the most predominant type [18, 19].

In the study of Al-Rahim et al, there is a prominence of male gender in the squamous cell carcinoma type and an equal distribution in male and female in the adenocarcinoma [18], while in our study; number of males is more than females in all NSCLC types, however; types of NSCLC were non-significantly associated with the age& gender (p-values>0.05).

Immunotherapy targeted against the programmed death ligand 1 (PD-L1) and their receptors (PD-1) had improved the prognosis in a group of patients with lung

cancer. So that, PD-L1 protein expression had considered as a biomarker predicting which patients will be more likely responding to immunotherapy [6].

In our study, 39 instances (41.5%) of NSCLC patients had positive IHC PD-L1 expression (⩾1%). In 12 cases (12.7%) of NSCLCs, there was high expression in ⩾50% of tumor cells. These findings are consistent with the research of Pawelczyk et al., which found that 10.6% of NSCLCs had high expression (⩾50%) and 32.5% of patients had positive IHC PD-L1 expression (⩾1%) [20]. However, compared to other studies, such as those by Tsunoda et al., which found high expression of (⩾50%) in 31.4%) of NSCLCs and positive IHC PD-L1 expression (⩾1%) in 62.8%) of NSCLC patients, and Dietel et al., which found that 22% of patients had PD-L1 TPS ⩾ 50%, 52% of patients had PD-L1 TPS ⩾ 1%, and 48% of patients had PD-L1 TPS < 1% [26]. Between 50% and 70% of patients of NSCLC were found to have positive PD-L1 expression [27–29]. Nevertheless, PD-L1 positive expression was detected in a significantly lower percentage in a few investigations [30–33]. The use of various scoring systems and evaluation cut-off values may contribute to the explanation of the variable expression of PD-L1 in NSCLC. Additionally, utilizing different antibody clones (22-8, 22C3, SP263, and SP142) may have contributed to the variations in the percentage of cases expressing PD-L1 in NSCLC tumor cells among investigations. The ethnic groups that were the subject of the research may also contribute to this variation. In our analysis, patients with Unclassifiable forms of non-small cell lung cancer had the highest PD-L1 expression levels, whereas patients with Adenosquamous types had the lowest values. Comparing the various categories based on the Mean PD-L1 levels revealed non-significant connections. While elevated PD-L1 expression was more frequently seen in large cell carcinomas (12.1%) and squamous cell carcinomas (8.1%) than in adenocarcinomas (5.1%) in a research by Cooper et al., this was not statistically significant (p=0.072) [30]. Our research revealed a non-significant negative correlation between age and PD-L1, with an increase in age connected with a decrease in PD-L1 Expression. This finding aligns with the research conducted by Cooper et al [30], which shown that a higher level of PD-L1 expression was linked to a younger patient age. While some research has identified a correlation between younger patient age and increased PD-L1 expression, other studies have not found any meaningful correlation. Depending on the study population and PD-L1 expression assessment methods, there may be differences in the connection between PD-L1 expression and clinicopathological variables. Consequently, while evaluating the findings, it's critical to take each study's limitations and context into account.

A substantial percentage of NSCLC expresses PD-L1 at high levels. To identify the patients who benefit from immunotherapy, immunohistochemistry is required. A lower patient age was correlated with higher PD-L1 expression.

Ethical Approval

The study was approved by the ethical committee of Al-Kindy College of Medicine (reference number 203) at 29\3\ 2023 and conducted by its institutional policy. As it was a retrospective study using data without violating patient privacy, consent to participate was deemed not applicable.

Author Contributions

Alaa Q. Yahya was responsible for the study design and conception while Zina A Rajab participated in data collection and analysis. Samir Z. Ahmed and Ahmad Fawzi Hussain were responsible for writing and preparing the draft of the article.

Conflict of Interest

No conflict of interest was declared by auhtors.

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