doi • 10.5578/tt.20229803
Tuberk Toraks 2022;70(2):132-140
Received/Geliş Tarihi: 27.01.2022 • Accepted/Kabul Ediliş Tarihi: 30.03.2022

RESEARCH ARTICLE
KLİNİK ÇALIŞMA

The relationship between clinicopathological parameters and PD-L1 expression level in advanced stage non-small cell lung cancer

Mustafa GÜRBÜZ[1] (ID)
İzzet DOĞAN[2] (ID)
Erman AKKUŞ[3] (ID)
Hilal ÖZAKINCI[4] (ID)
Pınar KUBİLAY TOLUNAY[1] (ID)
Ender KALACI[1] (ID)
Tolga BAĞLAN[4] (ID)
Elif Berna KÖKSOY[1] (ID)
Koray CEYHAN[4] (ID)
Serpil DİZBAY SAK[4] (ID)
Adnan AYDINER[2] (ID)
Ahmet DEMİRKAZIK[1] (ID)
Güngör UTKAN[1] (ID)

[1] Division of Medical Oncology, Ankara University Faculty of Medicine, Ankara, Turkey
[1] *Ankara Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Bilim Dalı, Ankara, Türkiye*
[2] Division of Medical Oncology, İstanbul University Faculty of Medicine, İstanbul, Turkey
[2] *İstanbul Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Bilim Dalı, İstanbul, Türkiye*
[3] Department of Internal Medicine, Ankara University Faculty of Medicine, Ankara, Turkey
[3] *Ankara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Ankara, Türkiye*
[4] Department of Pathology, Ankara University Faculty of Medicine, Ankara, Turkey
[4] *Ankara Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, Ankara, Türkiye*

Cite this article as: *Gürbüz M, Doğan İ, Akkuş E, Özakıncı H, Kubilay Tolunay P, Kalacı E, et al. The relationship between clinicopathological parameters and PD-L1 expression level in advanced stage non-small cell lung cancer. Tuberk Toraks 2022;70(2):132-140.*

Yazışma Adresi (Address for Correspondence)
Dr. Mustafa GÜRBÜZ
Division of Medical Oncology,
Ankara University Faculty of Medicine
ANKARA - TURKEY
e-mail: drgurbuz123@gmail.com

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ABSTRACT

The relationship between clinicopathological parameters and PD-L1 expression level in advanced stage non-small cell lung cancer

Introduction: *Clinicopathological parameters related to programmed death ligand 1 (PD-L1) expression levels have been investigated in several studies. However, the results of these studies are conflicting and vary in different populations. This study aimed to investigate the relation of clinicopathological parameters with PD-L1 expression level in advanced stage non-small cell lung cancer patients.*

Materials and Methods: *The patients diagnosed with non-small cell lung cancer were enrolled, retrospectively. The data of clinicopathological parameters was collected. Clinicopathological parameters in relation to PD-L1 expression levels (0%, 1-50%, and >50%) were analyzed as univariable and multivariable.*

Results: *In total, 384 patients were enrolled. PD-L1 expression in tumor cells was between 1-50%, and >50% in 41.4%, and 23.4% of patients, respectively. There was no PD-L1 expression in 35.2% of the patients. In univariable analysis, we found that the parameters associated with PD-L1 expression levels revealed that metastatic site number, the subtype of cancer, diagnostic material type, platelet number, and LDH level were statistically significant. Adenocarcinoma frequency was higher in tumors that had PD-L1 expression >50% than in tumors that did not express PD-L1 and the difference was sta-*

tistically significant (p= 0.04, coefficient= 0.3, 95% CI 0.09-0.94). Cytology as diagnostic material was significant in PD-L1 level 1-50% comparing to >50% (p= 0.02, coefficient= 2.2, 95% CI= 1.08-4.46).

Conclusion: *According to the results of our study, many of the clinicopathological parameters are not related to the PD-L1 level. The histological subtype and diagnostic material may affect the level of PD-L1 expression.*

Key words: *Programmed cell death ligand 1; non-small cell lung cancer; clinicopathological parameters; immunotherapy*

ÖZ

İleri evre küçük hücreli dışı akciğer kanserinde klinikopatolojik parametreler ile PD-L1 ekspresyon düzeyi arasındaki ilişki

Giriş: *Programlanmış ölüm ligandı 1 (PD-L1) ekspresyon düzeyleri ile ilgili klinikopatolojik parametreler çeşitli çalışmalarda araştırılmıştır. Ancak, bu çalışmaların sonuçları farklı popülasyonlarda çelişkili ve değişkendir. Bu çalışma, ileri evre küçük hücreli dışı akciğer kanseri hastalarında klinikopatolojik parametrelerin PD-L1 ekspresyon düzeyi ile ilişkisini araştırmayı amaçlamıştır.*

Materyal ve Metod: *İleri evre küçük hücreli dışı akciğer kanseri tanısı olan hastalar retrospektif olarak çalışmaya dahil edildi. Klinikopatolojik parametrelerin verileri toplandı. PD-L1 ekspresyon seviyeleri (%0, %1-50 ve >%50) ile ilişkili klinikopatolojik parametreler tek değişkenli ve çok değişkenli olarak analiz edildi.*

Bulgular: *Toplam 384 hasta çalışmaya dahil edildi. Tümör hücrelerinde PD-L1 ekspresyonu sırasıyla hastaların %41,4'ünde %1-50 ve %23,4'ünde >%50 idi. Hastaların %35,2'sinde PD-L1 ekspresyonu saptanmadı. Tek değişkenli analizde, PD-L1 ekspresyon seviyeleri ile metastatik bölge sayısı, kanser alt tipi, tanı materyal tipi, trombosit sayısı ve LDH seviyesinin istatistiksel olarak anlamlı düzeyde ilişkili olduğu gösterildi. PD-L1 ekspresyonu >%50 olan tümörlerde adenokarsinom sıklığı, PD-L1 ekspresyonu olmayanlara göre daha yüksekti ve fark istatistiksel olarak anlamlıydı (p= 0,04, katsayı= 0,3, %95 GA 0,09-0,94). PD-L1 ekpresyon düzeyi %1-50 ve >%50 karşılaştırıldığında tanı materyali olarak sitoloji %1-50 grupta anlamlı olarak fazlaydı (p= 0,02, katsayı= 2,2, %95 GA= 1,08-4,46).*

Sonuç: *Bizim çalışmamızda klinikopatolojik parametrelerin çoğu PD-L1 düzeyi ile ilişkili değildi. Histolojik alt tip ve tanı materyali, PD-L1 ekspresyonun düzeyini etkileyebilir.*

Anahtar kelimeler: *Programlanmış hücre ölüm ligandı 1; küçük hücreli dışı akciğer kanseri; klinikopatolojik parametreler; immünoterapi*

INTRODUCTION

Lung cancer is the second most common cancer type according to the GLOBOCAN 2020 data and accounts for 11.4% of all newly diagnosed cancers and 18% of the cancer-related deaths (1). It is divided into two main groups, small cell lung cancer and non-small cell lung cancer (NSCLC). Eighty percent of all lung cancers are NSCLC and are commonly diagnosed in the advanced stage. Identifying the histological subtype and analyzing biomarkers are necessary for optimal management. Although platin-based doublet chemotherapy was the standard therapy for lung cancers that are not eligible for targeted therapies, the immune checkpoint inhibitors have changed the daily practice in the last few years (2).

Programmed cell death ligand-1 (PD-L1) is the ligand of programmed cell death 1 (PD-1), which is expressed on the surface of immune cells. Programmed cell death ligand-1 enables cancer cells to be tolerant to immune cells, leading to proliferation and progression (3). The immune checkpoint inhibitors like nivolumab, pembrolizumab, atezolizumab, and durvalumab inhibit PD-1 and PD-L1 interaction and stimulate the immune response to NSCLC (4). However, not all patients respond to treatment. It is important to detect predictive biomarkers that identify the patients who will respond to therapy. Programmed cell death ligand-1 expression level which can be analyzed via immunohistochemistry has been shown to be a predictive biomarker (5).

Since analyzing the PD-L1 expression level requires pathological and immunohistochemistry (IHC) evaluation, and PD-L1 expression level is not perfect for prediction; clinicopathological parameters associated with PD-L1 expression levels have been investigated in several studies. Smoking, nodal metastasis, male gender, squamous cell subtype, peripheral blood parameters, K-RAS and EGFR mutations, and cavitation were associated with PD-L1 expression levels (6-10). However, the results of these studies are conflicting and vary in different populations. This study aimed to investigate the relation of clinicopathological parameters with PD-L1 expression levels in advanced NSCLC patients.

MATERIALS and METHODS

Patients and PD-L1 Expression Analysis

The study was designed as retrospective and two-centered. The NSCLC patients older than 18 years old, diagnosed between 2018 and 2021, with pathological tissue samples analyzed for PD-L1 expression level were included in the study. The data of the patients were collected from the hospital databases of the centers. The pathological examination has been performed, and the PD-L1 expression level was determined in each center locally. Data including age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), history of smoking, history of alcohol use, primary tumor localization, stage, histological subtype, number of metastatic sites, diagnostic material type (cytological sample or not), PD-L1 expression level, targeted mutations, complete blood count and metabolic panel results at the time of diagnosis were collected and analyzed as clinicopathological parameters. Pathologic tumor stage was defined based on the American Joint Committee on Cancer Staging Manual, 8th edition.

PD-L1 expression was evaluated by IHC using rabbit monoclonal anti-PD-L1 clone SP263 [Ventana Medical Systems, Inc., Tucson, Arizona, USA; retrieval: EDTA 60'; incubation: 120'; ready to use (RTU) dilution]. Human placental tissue was utilized as a positive control. Programmed cell death ligand-1 status was determined by the percentage of tumor cells with any membranous (partial or complete) +/- cytoplasmic staining. The characteristics of the entire study population and univariable and multivariable analysis of the association between clinicopathological parameters and PD-L1 expression levels were assessed. Next-generation sequencing (NGS) results for EGFR, BRAF, and KRAS; and immunohistochemical (+/- FISH) results for ALK, and ROS-1 genes were noted, where available.

Statistical Analysis

Continuous variables are given as median [minimum (min), maximum (max)], and categorical variables are presented as percentages. The relationship between variables and the PD-L1 expression levels was analyzed with Chi-square/Fisher exact test for categorical variables and Pearson/Spearman correlation test for continuous variables. Statistically significant variables were included in multinominal logistic regression for multivariable analysis. All p values were based on a 2-tailed test of significance (p= 0.05). SPSS version 22 was used for the analyses.

RESULTS

Patient Characteristics

In total, 384 patients were included in the study. The median age was 63 (range 31-87). 74.7% of the patients were male. 85% of the patients had an ECOG performance status of zero, one, or two. Median BMI was 25.2 (range 15.5-44.9). 17.4% of the patients did not have a smoking history, while the remainder had a median of 40 packets/year (range 5-100). 10.2% of the patients had a history of alcohol use. The primary tumor was localized in the right lung in 53.9% and the left lung in 36.5% of the patients. 2.1% of the patients had synchronous tumors in bilateral lungs. Metastatic and locally advanced stages were present in 55.2% and 28.1%, respectively. The median number of metastatic sites was 2 (range 1-5), and histological and cytological samples were used for diagnosis in 48.7% and 46.4% of the patients, respectively. 66.4% of the patients had adenocarcinoma, 20.1% SCC, and 13.5% NOS. Pogrammed death ligand 1 expression in tumor cells was between 1%-50% in 41.4%, and >50% in 23.4% of patients. There was no PD-L1 expression in 35.2% of the patients. Primary tumor samples were used to analyze PD-L1 expression levels in 55.7% of the patients. 71.4% of the patients did not have any molecular alteration related to targeted therapy. The proportion of patients with O, A, AB, and B blood types was 34.9%, 40.4%, 9.4%, and 15.3%, respectively. 85.7% of the patients were Rh positive (Table 1).

Clinicopathological Parameters and PD-L1 Expression Level

The PD-L1 expression level was grouped as 0%, 1%-50%, and >50%. Univariable analysis of the parameters in relationship with PD-L1 expression level revealed that the number of metastatic sites, cancer subtype, diagnostic material type, platelet count, and LDH level was statistically significant (Table 2). These parameters were included in the multivariable analysis. Adenocarcinoma frequency was higher in tumors that had PD-L1 expression >50% than in tumors that did not express PD-L1 and the difference was statistically significant (p= 0.04, coefficient= 0.3, 95% CI= 0.09-0.94). Cytology as diagnostic material was significantly different in PD-L1 level 1-50% compared to >50% (p= 0.02, coefficient= 2.2, 95% CI= 1.08-4.46).

Table 1. Baseline characteristics of the study population

n= 384	**n (%) median (min-max)**
Age (median, min-max)	63 (31-87)
Gender (n, %)	
Female	97 (25.3)
Male	287 (74.7)
ECOG (n, %)	
0	84 (21.9)
1	203 (52.9)
2	47 (12.2)
3	6 (1.6)
Unknown	44 (11.4)
BMI (median, min-max)	25.2 (15.5-44.9)
Smoking (n, %)	
Never	67 (17.4)
Ex-smoker	184 (47.9)
Current smoker	79 (20.6)
Unknown	54 (14.1)
Smoking pack/year (median, min-max)	40 (5-100)
Alcohol history (n, %)	
Yes	39 (10.2)
No	284 (74)
Unknown	61 (15.8)
Primary tumor localization (n, %)	
Right	207 (53.9)
Left	140 (36.5)
Bilateral	8 (2.1)
Unknown	29 (7.5)
Stage (n, %)	
Metastatic	212 (55.2)
Locally advanced	108 (28.1)
Unknown	64 (16.7)
Metastatic site number (median, min-max)	2 (1-5)
Histological subtype (n, %)	
Adenocarcinoma	255 (66.4)
SCC	77 (20.1)
NOS	52 (13.5)
Diagnostic material (n, %)	
Cytology	178 (46.4)
Histology	187 (48.7)
Unknown	19 (4.9)
PD-L1 expression (n, %)	
0	135 (35.2)
1-50	159 (41.4)
>50	90 (23.4)

Table 1. Baseline characteristics of the study population (continue)

	n= 384
PD-L1 analysis material (n, %)	
Primary tumor	214 (55.7)
Lymph node	77 (20.1)
Metastatic tumor	81 (21.1)
Body fluid	8 (2.1)
Unknown	4 (1)
Other mutations (n, %)	
No	274 (71.4)
EGFR	27 (7)
ALK	17 (4.4)
ROS1	8 (2.1)
BRAF	9 (2.3)
Unknown	49 (12.8)
CBC (median, min-max)	
Leukocyte/ uL	8955 (2840-29.700)
Neutrophile/ uL	6015 (1220-25.600)
Lymphocyte/ uL	1695 (340-5140)
Platelet/ mL	321 (100-828)
MPV (fL)	9.5 (5.9-13.5)
Hb (g/dL)	13.3 (7-18.7)
MCV (fL)	85.9 (60.1-99.9)
Chemistry (median, min-max)	
LDH (IU/L)	203 (73-911)
Albumin (g/dL)	3.9 (1.95-5)
CRP (mg/L)	16.9 (0.18-311)
ABO (n, %)	
O	134 (34.9)
A	155 (40.4)
AB	36 (9.4)
B	59 (15.3)
Rh (n, %)	
Positive	329 (85.7)
Negative	55 (14.3)

ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, CBC: Complete blood count.

These results suggest that the adenocarcinoma subtype is related to higher expression of PD-L1 and cancer diagnosis using cytological sample is higher in 1-50% level than >50% level. There was no relationship between PD-L1 expression level and EGFR, ALK, ROS-1, and B-RAF mutations (Table 3).

DISCUSSION

To the best of our knowledge, this is the first study investigating the relationship between clinicopathological parameters and PD-L1 expression level in NSCLC in our country. PD-L1 expression in tumor cells was between 1%-50%, and >50% in 41.4%, and 23.4% of patients, respectively. There was no PD-L1 expression in 35.2% of the patients. Adenocarcinoma is related to higher expression of PD-L1 and PD-L1 analysis by using cytological sample is higher in 1-50% level than >50% level.

The study in Tokyo Metropolitan Cancer and Infectious Diseases Centre, Komagome Hospital, studied 108 NSCLC patients retrospectively and

Table 2. Univariable analyses of clinicopathological parameters-PD-L1 expression level

Variable	PD-L1 expression levels (0%, 1-50%, >50%)	
	Test statistic (Chi-square/Fisher test statistics or correlation coefficient*)	p
Age*	-0.012	0.81
Gender	0.66	0.71
ECOG	2.15	0.90
BMI*	-0.029	0.66
Smoking	2.48	0.64
Pack/year*	0.03	0.63
Alcohol	4.1	0.13
Primary tumor	5.07	0.52
Stage	4.31	0.11
Metastatic site number*	**-0.11**	**0.03**
Subtype		
Adenocarcinoma	**12.92**	**0.01**
SCC		
NOS		
Diagnostic material		
Cytology	**15.1**	**0.003**
Histology		
PD-L1 material	9.08	0.33
Other mutations	8.64	0.56
Leukocyte*	0.05	0.33
Neutrophile*	0.03	0.48
Lymphocyte*	0.01	0.83
Hb*	0.01	0.78
MCV*	0.02	0.62
PLT*	**0.1**	**0.03**
MPV*	0.03	0.59
LDH*	**-0.17**	**0.002**
Albumin*	-0.01	0.81
CRP*	-0.04	0.44
ABO	5.33	0.50
Rh	2.77	0.25

*Continuous variables (test statistic is correlation coefficient). Statistically significant results were written bold. Hb: Hemoglobin, PLT: Platelet, MPV: Mean platelet volume, LDH: Lactic acid dehydrogenase, CRP: C-reactive protein.

found that lymph node metastasis was associated with positive PD-L1 expression and sample preservation and high carcinoembryonic antigen (CEA) levels were associated with negative expression (11). In our study, there was no difference among the materials on which PD-L1 was studied. Also, we did not evaluate baseline tumor markers of the patients due to a lack of available information.

A study of 78 patients revealed that alterations in PD-1/PD-L1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4) expression at the mRNA level in lung tumoral tissue are unrelated to age and sex smoking status, histological type, pathological stage, and tumor differentiation degree (12). In another study investigating molecular alterations, clinicopathological parameters, and PD-L1 expression levels, 53.6%

Table 3. Multivariable analyses of clinicopathological parameters-PD-L1 expression level

Variable	PD-L1= 0%	PD-L1= 1%-50%	PD-L1= >50%	PD-L1= 0% vs 1-50%		PD-L1= 0% vs >50%		PD-L1= 1-50% vs >50%	
				Coefficient (95% CI)	P	*Coefficient (95% CI)*	P	*Coefficient (95% CI)*	P
Number of metastatic sites (median, min-max)	2 (1-4)	2 (1-5)	2 (1-4)	1.11 (0.75-1.63)	0.58	1.3 (0.85-1.99)	0.21	1.17 (0.79-1.74)	0.42
Histological subtype (n, %)									
Adenocarcinoma									
SCC	81 (60)	110 (69.2)	64 (71.1)	0.43 (0.16-1.16)	0.09	**0.3 (0.09-0.94)**	**0.04**	0.7 (0.21-2.32)	0.56
vs	24 (17.8)	35 (22)	18 (20)	0.28 (0.07-1.08)	0.06	0.37 (0.07-1.79)	0.21	1.32 (0.29-5.95)	0.71
NOS	30 (22.2)	14 (8.8)	8 (8.9)						
Diagnostic material (n, %)									
Cytology	48 (39)	87 (58)	43 (48)	Na	0.99	Na	0.99	**2.2 (1.08-4.46)**	**0.02**
vs	76 (61)	64 (42)	46 (52)						
Histology									
Platelet (median, min-max)	297 (100-828)	298 (107-722)	324 (171-636)	0.99 (0.99-1)	0.30	0.99 (0.99-1)	0.08	0.99 (0.99-1)	0.40
LDH (median, min-max)	220 (73-911)	204 (80-872)	191 (120-512)	1 (0.99-1)	0.73	1 (1-1)	0.08	1 (0.99-1)	0.13

Statistically significant results were written bold. LDH: Lactic acid dehydrogenase.

of the patients had PD-L1 expression levels ≥%1. Positive PD-L1 expression was detected higher in patients with genetic alterations. Furthermore, both PD-L1 positivity and high PD-L1 expression (≥50%) had statistically significant associations with Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations. However, there was no relationship between histological subtypes, clinicopathological parameters, and PD-L1 level (13). Our study did not find any relationship between PD-L1 expression level and EGFR, ALK, ROS-1, and B-RAF mutations.

In contrast to our findings, a Korean study found that PD-L1 expression was significantly higher in squamous cell cancer than in adenocarcinoma (14). In another study with 404 lung adenocarcinoma patients; advanced stage, lymph node metastasis, solid predominant subtype, and wild type epidermal growth factor receptor (EGFR) were associated with PD-L1 expression levels (15). A study has shown that biopsy and cytological specimens did not show different PD-L1 expression rates (16). The detection of PD-L1 level 1-50% was higher than level >50% by the cytologic sample in our study.

Our study has some limitations. First, the study was designed retrospectively. Secondly, there is no other molecular alteration data like HER2, and RET other than EGFR, ALK, ROS-1, and B-RAF. Thirdly, the pathological examination and PD-L1 expression level analysis were performed locally in the centers, which may cause variability. The results from PD-L1 SP263 assays may be different from other assays.

CONCLUSION

Our study reveals that many clinicopathological parameters are not related to the PD-L1 level in advanced NSCLC. The histological subtype and diagnostic material may affect the detection of PD-L1 expression and may have an important role in the treatment decision. These results may be beneficial for selecting high-risk patients for a good response to the immunotherapy and there is a need for studies that will confirm our results involving large patient groups on this subject.

Ethical Committee Approval: Ethics committee approval was obtained from the Ankara University Faculty of Medicine Ethics Committee in compliance with the Helsinki Declaration (Decision No: İ5-277-20, Date: 15.05.2020).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MG, İD, EA, GU

Analysis/Interpretation: MG, EA

Data acqusition: All of authors

Writing: MG, İD, EA, EBK

Clinical Revision: MG, İD, EA, EBK, AD, GU

Final Approval: GU

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