

Research Article

Association Between Smoking Status and PD-L1 Expression in Metastatic Driver Mutation Negative Non-Small Cell Lung Cancer: A Real-World Cohort Study

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Abstract

Objectives: Programmed cell death-1 (PD-L1) expression has become a key predictive biomarker for immunotherapy; however, the clinical and biological factors influencing its expression remain incompletely understood. Tobacco smoking is associated with extensive genomic alterations and increased tumor mutational burden (TMB), which may influence immune checkpoint signaling and tumor immunogenicity.

Methods: In this retrospective observational study, patients with stage IV driver-mutation-negative NSCLC treated at a tertiary oncology center were included. Clinical and pathological variables including age, sex, smoking status, histological subtype, Eastern Cooperative Oncology Group performance status, and PD-L1 expression were collected from institutional medical records. PD-L1 expression was evaluated using immunohistochemistry and reported as tumor proportion score (TPS), categorized as <1%, 1–49%, and ≥50%. Associations between smoking status and PD-L1 expression were analyzed using the chi-square test, and multivariable ordinal logistic regression was performed to identify independent predictors of PD-L1 expression.

Results: A total of 333 patients with stage IV driver-mutation-negative NSCLC were included in the analysis. High PD-L1 expression (TPS ≥50%) was observed in 32 (43.2%) current smokers, compared with 18 (10.8%) former smokers and 4 (4.3%) never smokers, with a significant association between smoking status and PD-L1 expression categories ($p<0.001$). In multivariable ordinal logistic regression analysis adjusted for age, sex, and histological subtype, smoking status remained independently associated with higher PD-L1 expression (OR: 3.53, 95% CI: 2.44–5.11, $p<0.001$).

Conclusion: Smoking status was independently associated with PD-L1 expression in patients with stage IV driver-mutation-negative NSCLC.

Keywords: Biomarkers, immune checkpoint inhibitors, non-small cell lung cancer, PD-L1, smoking, tumor mutational burden

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Lung cancer remains the leading cause of cancer-related mortality worldwide and represents a major global health burden. According to the most recent Global Cancer Observatory (GLOBOCAN) 2022 estimates, approximately 20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide in 2022. Lung cancer accounted for nearly 2.48 million new cases (12.4% of all cancers) and approximately 1.8 million deaths, making it both the most frequently diagnosed cancer and the leading cause of cancer-related mortality globally.^[1,2] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and represents the predominant histological category of the disease. The major histological subtypes of NSCLC include adenocarcinoma and squamous cell carcinoma, with adenocarcinoma being the most frequently diagnosed subtype.^[3]

Over the past decade, the development of immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1) receptor and its ligand programmed death-ligand 1 (PD-L1) has fundamentally transformed the therapeutic landscape of advanced NSCLC. These agents restore anti-tumor immune responses by blocking inhibitory immune checkpoint signaling pathways that enable tumor cells to evade immune surveillance.^[4,5]

PD-L1 expression assessed by immunohistochemistry has emerged as the most widely used predictive biomarker for selecting patients who may benefit from immune checkpoint inhibitors. Higher PD-L1 expression levels have consistently been associated with improved responses to PD-1 or PD-L1 blockade in patients with advanced NSCLC.^[6,7]

Despite its clinical relevance, PD-L1 expression demonstrates substantial heterogeneity among tumors and may be influenced by multiple biological and clinicopathological factors. These include tumor histology, oncogenic driver mutations, tumor mutational burden, and features of the tumor immune microenvironment.^[8]

Large genomic studies have demonstrated that lung cancers arising in smokers harbor significantly higher mutational loads compared with tumors in never smokers. Tobacco exposure produces characteristic mutational signatures that reflect the carcinogenic effects of tobacco smoke.^[9] Tumors with increased mutational burden often generate higher numbers of neoantigens, which can enhance tumor immunogenicity and activate immune checkpoint pathways including PD-L1 upregulation. This adaptive immune resistance mechanism represents an important strategy by which tumors evade immune-mediated destruction.^[8,10]

Several studies have suggested a potential association between smoking history and PD-L1 expression in NSCLC. For example, Takada et al.^[11] reported that smoking status was

independently associated with increased PD-L1 expression in patients with NSCLC. Similarly, meta-analyses and observational studies have demonstrated that PD-L1 expression may be associated with several clinicopathological characteristics including smoking status, tumor stage, and histological subtype.^[12,13]

Although these findings suggest a potential biological link between tobacco exposure and immune checkpoint regulation, the relationship between smoking status and PD-L1 expression remains incompletely understood and findings across studies have been inconsistent. Furthermore, data specifically focusing on patients with advanced driver-mutation-negative NSCLC, a population in which immune checkpoint inhibitors represent a major therapeutic strategy, remain limited. Real-world data evaluating the association between smoking exposure and PD-L1 expression in this population remain scarce.

Therefore, the aim of the present study was to investigate the association between smoking status and PD-L1 expression in a real-world cohort of patients with stage IV driver-mutation-negative NSCLC.

Methods

Study Design and Patient Population

This retrospective observational study included patients with stage IV NSCLC who were diagnosed or treated at the Department of Medical Oncology, Etlik City Hospital Hospital, between October 1, 2022, and October 10, 2025. Clinical data were retrospectively obtained from the hospital information management system and institutional medical records. All patients included in the study had metastatic (stage IV) disease. Stage IV disease was determined using thoracic and abdominopelvic computed tomography (CT), with positron emission tomography/computed tomography (PET/CT) and brain imaging using CT or magnetic resonance imaging (MRI) performed when clinically indicated.

To reduce biological heterogeneity and better evaluate the association between smoking status and immune checkpoint signaling, only patients with driver-mutation-negative tumors were included in the analysis. EGFR, ALK, and ROS1 alterations were assessed as part of routine institutional diagnostic practice using available validated molecular and/or pathological methods; next-generation sequencing (NGS) was not routinely used during the study period. Patients with documented EGFR mutations, ALK rearrangements, or ROS1 rearrangements were excluded. This approach allowed the study to focus on a clinically relevant population in which immune checkpoint inhibitors represent a major systemic treatment strategy.

Patients were required to have histologically confirmed NS-CLC and available PD-L1 expression results obtained from tumor tissue samples. Patients with incomplete clinical data or unavailable PD-L1 assessment were excluded from the analysis.

The study was conducted in accordance with the Declaration of Helsinki.

Data Collection

Clinical and pathological data were retrospectively collected from institutional electronic medical records. The following variables were recorded for each patient:

- age at diagnosis
- sex
- smoking status
- histological subtype
- ECOG performance status
- PD-L1 expression level

Smoking status was determined from the smoking history documented in the medical records at the time of diagnosis. Patients who had never smoked were classified as never smokers, those who had previously smoked but had stopped smoking before diagnosis were classified as former smokers, and those who were actively smoking at the time of diagnosis were classified as current smokers. Because the exact duration of smoking cessation was not consistently documented in the retrospective medical records, no minimum cessation period was required to classify patients as former smokers.

Histological classification included adenocarcinoma, squamous cell carcinoma, and other histological subtypes.

PD-L1 Assessment

PD-L1 expression was evaluated using immunohistochemical staining performed on formalin-fixed paraffin-embedded tumor tissue samples according to institutional pathology protocols. PD-L1 staining was performed using the VENTANA PD-L1 (SP263) assay (Ventana Medical Systems, Roche Diagnostics) on an automated immunohistochemistry platform. PD-L1 expression was reported as the tumor proportion score (TPS), defined as the percentage of viable tumor cells demonstrating membranous PD-L1 staining.

For statistical analysis, PD-L1 expression was categorized into three clinically relevant groups:

- PD-L1 <1%
- PD-L1 1–49%
- PD-L1 ≥50%

Statistical Analysis

Continuous variables were expressed as median with interquartile range (IQR), while categorical variables were reported as numbers and percentages.

Associations between smoking status and PD-L1 expression categories were evaluated using the chi-square test. The Kruskal–Wallis test was used to compare the distribution of PD-L1 tumor proportion scores across the three smoking-status groups.

For the multivariable ordinal logistic regression analysis, smoking status was entered as an ordered variable coded as never smoker=0, former smoker=1, and current smoker=2. Accordingly, the reported odds ratio for smoking status represents the change in the odds of belonging to a higher PD-L1 expression category for each one-category increase in smoking status. Because smoking status was modeled as a single ordered variable, no separate reference category was used.

To determine whether smoking status was independently associated with PD-L1 expression, a multivariable ordinal logistic regression model was constructed. The proportional odds assumption was assessed using the test of parallel lines, and no violation was detected. Multicollinearity was evaluated using variance inflation factors (VIFs), and no significant collinearity was observed. The multivariable model included age, sex, and histological subtype as covariates.

Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided $p < 0.05$ was considered statistically significant.

All statistical analyses were performed using standard statistical software.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

Ethics Statement

Ethics approval was obtained from the institutional ethics committee of Etlik City Hospital Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the ethics committee.

AI-Assisted Technologies Disclosure

The authors declare that no artificial intelligence (AI)-assisted technologies, including large language models (LLMs), chatbots, or image generation tools, were used in the preparation of this manuscript.

Results

A total of 333 patients with stage IV driver-mutation-negative NSCLC were included in the analysis. The median age of the study population was 66 years (IQR 57–68), and the majority of patients were male (n=276, 82.9%). Adenocarcinoma represented the most common histological subtype (n=148, 44.3%), followed by squamous cell carcinoma (n=129, 38.6%). Most patients had an ECOG performance status of 0–1 at the time of diagnosis (n=325, 97.7%).

Baseline demographic and clinicopathological characteristics of the study population are summarized in Table 1.

The distribution of PD-L1 tumor proportion score according to smoking status is presented in Table 2. Among never smokers (n=93), 67 patients (72.0%) had PD-L1 TPS <1%, 22 (23.7%) had TPS 1–49%, and 4 (4.3%) had TPS ≥50%. Among former smokers (n=166), the corresponding numbers were 111 (66.9%), 37 (22.3%), and 18 (10.8%), respectively. In contrast, among current smokers (n=74), 18 patients (24.3%) had PD-L1 TPS <1%, 24 (32.4%) had TPS 1–49%, and 32 (43.2%) had TPS ≥50%. The association between smoking status and PD-L1 expression categories was statistically significant (p<0.001).

The distribution of PD-L1 tumor proportion scores across smoking groups is illustrated in Figure 1, demonstrating a clear shift toward higher PD-L1 expression among current smokers, whereas lower PD-L1 expression predominated among never and former smokers. Figure 2 further illustrates the proportional distribution of PD-L1 expression categories within each smoking group, showing that PD-L1-negative tumors (TPS <1%) constituted the majority of cases among never and former smokers, while high PD-L1 expression (TPS ≥50%) represented the largest category among current smokers.

According to the multivariable ordinal logistic regression analysis, smoking status remained independently associated with higher PD-L1 expression after adjustment for age, sex, and histological subtype (OR: 3.53, 95% CI: 2.44–5.11, p<0.001). In contrast, age (OR: 1.01, 95% CI: 0.99–1.03, p=0.24), male sex (OR: 0.88, 95% CI: 0.51–1.52, p=0.64), and squamous histology (OR: 1.29, 95% CI: 0.87–1.92, p=0.19) were not significantly associated with PD-

Table 1. Baseline characteristics of the study population

Variable	Overall (n=333)
Age, median (IQR)	66 (57–68)
Sex	
Male	276 (82.9%)
Female	57 (17.1%)
Smoking Status	
Never smoker	93 (27.9%)
Former smoker	166 (49.8%)
Current smoker	74 (22.2%)
Histology	
Adenocarcinoma	148 (44.3%)
Squamous cell carcinoma	129 (38.6%)
Other	56 (16.8%)
ECOG Performance Status	
0–1	325 (97.7%)
≥2	8 (2.3%)
PD-L1 Expression	
<1%	196 (58.9%)
1–49%	83 (24.9%)
≥50%	54 (16.2%)

PD-L1: Programmed death-ligand 1; ECOG: Eastern Cooperative Oncology Group.

L1 expression. These findings indicate that smoking status was the only variable independently associated with higher PD-L1 expression in the multivariable model. The detailed results of the multivariable ordinal logistic regression analysis are presented in Table 3 and graphically illustrated in Figure 3.

Discussion

In this retrospective cohort of patients with stage IV driver-mutation-negative NSCLC, smoking status was strongly associated with PD-L1 expression. Current smokers demonstrated a markedly higher prevalence of high PD-L1 levels (TPS ≥50%) compared with former and never smokers, and smoking remained independently associated with increased PD-L1 expression after adjustment for clinico-

Table 2. Association between smoking status and PD-L1 expression

Smoking Status	PD-L1 <1%	PD-L1 1–49%	PD-L1 ≥50%
Never smoker (n=93)	67 (72.0%)	22 (23.7%)	4 (4.3%)
Former smoker (n=166)	111 (66.9%)	37 (22.3%)	18 (10.8%)
Current smoker (n=74)	18 (24.3%)	24 (32.4%)	32 (43.2%)

Chi-square test: p<0.001, PD-L1: Programmed death-ligand 1.

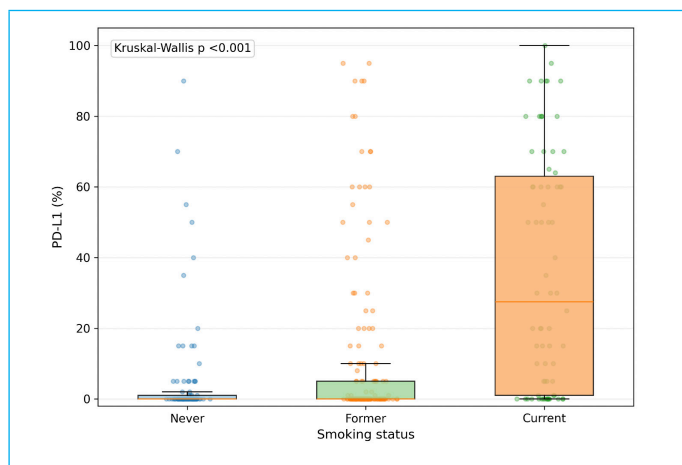


Figure 1. Distribution of PD-L1 expression according to smoking status.

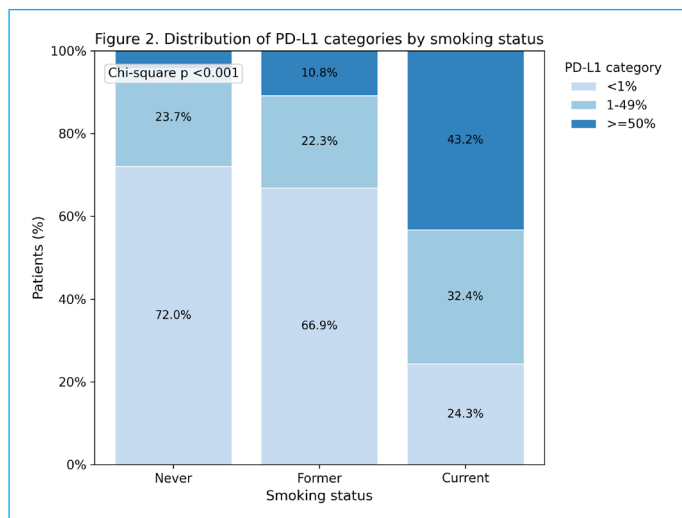


Figure 2. Distribution of PD-L1 categories across smoking groups.

pathological variables. These findings support the growing evidence that tobacco-associated lung cancers exhibit distinct tumor immunobiology characterized by enhanced neoantigen generation and activation of adaptive immune resistance mechanisms such as PD-L1 upregulation.^[14]

The association between smoking and PD-L1 expression is biologically plausible and likely reflects smoking-induced

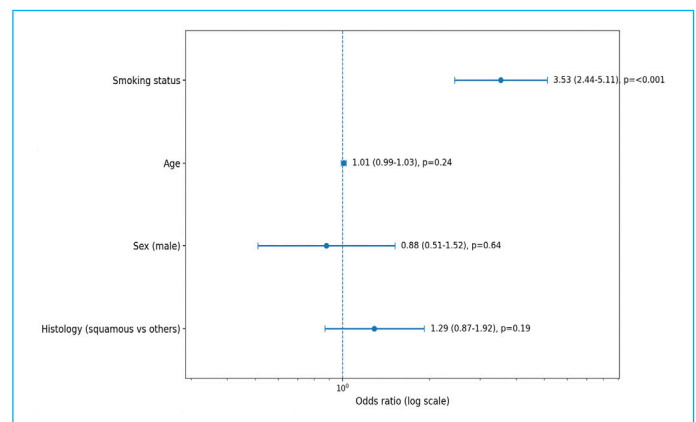


Figure 3. Multivariable analysis of factors associated with PD-L1 expression.

genomic alterations. Smoking-associated tumors exhibit substantially higher TMB compared with tumors arising in never smokers.^[15] Tobacco carcinogens generate extensive DNA damage and characteristic mutational signatures that increase TMB. Tumors with higher TMB produce a larger repertoire of neoantigens capable of stimulating antitumor immune responses within the tumor microenvironment. Under sustained immune pressure, tumor cells may upregulate PD-L1 as part of adaptive immune resistance. Large genomic studies have consistently shown that smoking-associated lung cancers harbor higher TMB and greater immunogenicity than tumors arising in never smokers.^[10,16]

Smoking-associated lung cancers frequently exhibit an immune-inflamed phenotype characterized by increased CD8+ T-cell infiltration, macrophage recruitment, and interferon signaling.^[17] These immune cells produce cytokines such as interferon- γ , which activates intracellular signaling pathways that induce PD-L1 expression on tumor cells. This adaptive response represents a key immune escape mechanism that allows tumor cells to evade immune-mediated destruction while maintaining immune engagement within the tumor microenvironment.^[18,19]

Recent mechanistic studies further support the link between tobacco exposure and immune checkpoint activation. Cigarette smoke induces oxidative stress, DNA adduct

Table 3. Multivariable ordinal logistic regression analysis for PD-L1 expression

Variable	Odds Ratio	95% CI	p
Smoking status	3.53	2.44–5.11	<0.001
Age	1.01	0.99–1.03	0.24
Sex (male)	0.88	0.51–1.52	0.64
Histology (squamous vs others)	1.29	0.87–1.92	0.19

OR: Odds ratio; CI: Confidence interval.

formation, and genomic instability, which activate innate immune pathways such as the cGAS–STING axis.^[20] Activation of this pathway links DNA damage to type-I interferon signaling and promotes immune activation within tumors. In addition, smoking can alter antigen presentation and dendritic cell activation, thereby enhancing T-cell priming and promoting an immune-inflamed tumor phenotype. These molecular mechanisms may collectively contribute to the higher prevalence of PD-L1 expression observed in smoking-associated lung cancers.^[21]

Previous studies evaluating the association between smoking and PD-L1 expression in NSCLC have produced heterogeneous results. While several observational studies reported higher PD-L1 expression among smokers, others failed to demonstrate a consistent relationship. Differences in patient populations, tumor stage distribution, histological composition, and PD-L1 testing methods may partly explain these discrepancies. Importantly, many earlier studies included heterogeneous populations comprising both early-stage and metastatic disease as well as tumors harboring oncogenic driver alterations, which may confound immune biomarker analyses.^[13]

Our analysis focused specifically on metastatic driver-mutation-negative NSCLC, a clinically relevant population in which immune checkpoint inhibitors represent a cornerstone of systemic therapy. Excluding tumors with oncogenic driver alterations allowed a more homogeneous evaluation of smoking-related tumor immunobiology. Driver-mutated tumors often exhibit lower TMB and reduced immune infiltration compared with smoking-associated tumors, which may partly explain differences in response to immune checkpoint blockade across molecular subtypes of lung cancer.^[22,23]

From a clinical perspective, our findings should be interpreted strictly as an association between smoking status and PD-L1 expression. The present study did not evaluate immunotherapy response, progression-free survival, or overall survival; therefore, no conclusions regarding differential treatment benefit according to smoking status can be drawn from these data. Further studies incorporating treatment and survival outcomes are required to determine the clinical significance of the observed association.^[24]

Another strength of the present study is the use of real-world clinical data from a relatively large cohort of metastatic NSCLC patients. Real-world evidence complements findings from randomized trials by reflecting biomarker distribution and treatment patterns in routine clinical practice. Such analyses may improve our understanding of biomarker variability and inform biomarker-guided treatment strategies in everyday oncology practice.^[25]

Several limitations should be acknowledged. First, the retrospective design may introduce selection bias and limits causal inference. Second, smoking exposure was classified based on clinical records and quantitative measures such as pack-year history were not available. Third, molecular biomarkers including TMB, genomic mutational signatures, and tumor-infiltrating lymphocytes were not assessed, limiting further mechanistic interpretation. In addition, variability among PD-L1 immunohistochemistry assays and potential intratumoral heterogeneity of PD-L1 expression may have influenced biomarker assessment. Finally, the single-center design may limit the generalizability of the findings.

Conclusion

Despite these limitations, our study provides additional real-world evidence demonstrating a significant association between smoking status and PD-L1 expression in metastatic driver-mutation-negative NSCLC. These findings contribute to the understanding of factors associated with variability in PD-L1 expression. Future prospective studies incorporating treatment response, progression-free survival, overall survival, genomic profiling, and characterization of the tumor immune microenvironment are warranted to determine the clinical significance of this association.

Disclosures

Ethics Committee Approval: The study was approved by the Etlik City Hospital Ethics Committee (no: AEŞH-BADEK1-2025-569, date: 22.10.2025).

Informed Consent: Informed consent was waived due to the retrospective nature of the study and the use of anonymized patient data.

Conflicts of Interest: The authors declared no conflicts of interest.

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Use of AI for Writing Assistance: The authors declared that no artificial intelligence (AI)-assisted technologies, including large language models (LLMs), chatbots, or image generation tools, were used in the preparation of this manuscript.

Authorship Contributions: Concept – SÇ, TE, EZ; Design – SÇ; Supervision – TE; Fundings – SK, Materials – SÇ, SK; Data Collection or Processing: SÇ; Analysis or Interpretation: EZ; Literature Search: ÖKK; Writing: SÇ, TE, EZ; Critical Review: SK.

Peer-review: Externally peer-reviewed.

Abbreviations

NSCLC	non-small cell lung cancer
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
TMB	tumor mutational burden
TPS	tumor proportion score
ECOG	Eastern Cooperative Oncology Group

OR odds ratio
 CI confidence interval
 IQR interquartile range

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