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PDL1 IMMUNOHISTOCHEMICAL EXPRESSION IN NON-SMALL CELL LUNG CANCER AND IT CLINICOPATHOLOGICAL CORRELATIONS

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ABSTRACT

Background: Programmed death ligand-1 (PD-L1) is a 33 kDa type 1 transmembrane protein that suppresses the adaptive immune response. Its interaction with programmed death-1 (PD-1) receptor inhibits cytokine production and contributes to immune evasion by tumor cells, playing a significant role in the progression of lung cancer. **Objective:** This study aimed to evaluate PD-L1 expression in non-small cell lung cancer (NSCLC) patients and its correlation with histopathological grade, tumor type, patient age, and gender. **Materials and Methods:** A retrospective study with prospective continuation was conducted on 62 histologically diagnosed NSCLC cases over six months at the Babylon Training Center of Pathology. PD-L1 immunohistochemical expression was assessed and scored using the Tumor Proportion Score (TPS). Statistical correlations were analyzed between PD-L1 expression and patient age, gender, tumor type, and histopathological grade. **Results:** This study comprised 62 NSCLC patients, 77.4% of whom were men, with a mean age of 63.68 years. PD-L1 expression and cancer grade were strongly correlated with squamous cell carcinoma, where all PD-L1-positive patients were moderately or poorly differentiated ($p = 0.02$). No association was seen between gender and adenocarcinoma grade ($p = 0.09$). Among the 62 NSCLC cases, 43.5% exhibited PD-L1 positivity. A statistically significant correlation was observed between PD-L1 expression and both patient age and tumor grade, indicating higher expression in older patients and poorly differentiated tumors. Among the PD-L1 positive cases, 63.0% demonstrated low expression, while 37.0% showed high expression. However, TPS levels did not significantly correlate with any of the studied clinicopathological parameters. Conclusion: In NSCLC, PD-L1 expression was highly linked to worse differentiation. Age was significantly correlated, although gender and tumour histological subtype (SCC vs. adenocarcinoma) were not.

KEYWORDS: PDL1, Immunohistochemical, Expression, Non-Small Cell, Lung Cancer.

INTRODUCTION

For the past four decades, platinum-based systemic chemotherapy has been the cornerstone of treatment for advanced-stage lung cancer; however, it has resulted in a median survival of only 12 months.[1] Approximately 40% of non-small cell lung cancer (NSCLC) patients harbor oncogenic mutations that present opportunities for targeted therapies. Therapeutic agents directed against driver mutations such as EGFR, ALK, and ROS-1 have demonstrated improved clinical outcomes compared to traditional chemotherapy.[2] In recent years, the blockade of programmed death receptor 1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), has emerged as a promising immunotherapeutic strategy for NSCLC.[3] PD-1, expressed on activated T cells, and PD-L1, expressed on tumor cells, constitute key immune checkpoint proteins. Overexpression of these molecules facilitates immune evasion by tumor cells, promoting tumor progression and metastasis.[3] The development of monoclonal antibodies targeting PD-1/PD-L1 has formed the basis for immunotherapy in NSCLC patients. According to the National Comprehensive Cancer Network (NCCN) guidelines, metastatic NSCLC patients with negative driver mutation status and positive PD-L1 expression are eligible for pembrolizumab, an anti-PD-1 monoclonal antibody, as a first-line monotherapy.[4] Reported prevalence rates of PD-L1 expression among NSCLC patients range from 13% to 70%.[5] A recent

meta-analysis has highlighted that PD-L1 expression levels vary based on clinical characteristics, tumor histology, and histopathological grade.[6] In the present study, we conducted immunohistochemical (IHC) analysis of PD-L1 expression in 62 NSCLC cases and examined its correlation with various clinicopathological parameters. The aim of study is to evaluation of programmed cell death ligand 1 immunohistochemical expression in non-small cell lung cancer and its correlation with different clinical and histopathological parameters.

METHOD

A retrospective with prospective continuation cross-sectional study was conducted at the Babylon Training Center of Pathology, including 62 confirmed non-small cell lung carcinoma (NSCLC) cases—48 males and 14 females. The sample size was calculated using standard statistical formulas considering ratio (r), average proportion exposed (p), desired power ($Z\beta = 0.84$), significance level ($Z\alpha = 1.96$), and expected effect size (P1–P2). Cases were collected between March and September 2024 from Hilla Teaching Hospital, Al-Sadiq Hospital, and private laboratories. Clinicopathological data including age, gender, tumor type, and tumor grade were obtained, and biopsy methods included FOB, core biopsy, and Tru-Cut biopsy; surgical biopsies were excluded. Inclusion Criteria: Patients of any age or gender diagnosed with NSCLC (squamous cell carcinoma or adenocarcinoma) with available paraffin blocks. Exclusion Criteria: Small cell lung cancer, other neuroendocrine tumors, adenosquamous carcinoma, large cell carcinoma, benign conditions, and cell blocks. Histological and Immunohistochemical Methods: Two 4µm tissue sections were obtained per sample; one underwent H&E staining, the other immunohistochemistry for PD-L1 expression using the 22C3 monoclonal antibody. Equipment and reagents from established manufacturers (e.g., Dako, Leica, Olympus) were used. Immunostaining followed manufacturer protocols, including target retrieval at pH 6.1 and use of control slides. Scoring: PD-L1 expression was quantified using Tumor Proportion Score (TPS):

TPS (%) = (PD-L1 positive tumor cells / Total viable tumor cells) × 100

Only membrane staining of viable tumor cells was considered; cytoplasmic staining and staining of immune cells were excluded. A minimum of 100 viable tumor cells was required for valid scoring. Statistical Analysis: Data were analyzed using SPSS v27. Categorical variables were presented as frequencies and percentages; continuous variables as means ± SD. Associations were tested using Chi-square or Fisher's exact test, and group comparisons used Student's t-test. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Our study covered 62 patients diagnosed with non-small cell lung cancer, categorized into five age groups: under 50 years, 50–60 years, 60–70 years, 70–80 years, and ≥80 years or older. The mean age of patients was 63.68 ± 11.21 years, with the oldest patient being 85 years and the youngest 31 years. Only five patients (8.1%) were in the age group of 80 years or older, as illustrated in Table 1.

Table 1: Distribution of patients with non-small carcinoma according to age (N=62)

Age (years)	Number	%
< 50 years	4	6.5%
50-60 years	16	25.7%
61-70 years	17	27.4%
71-80 years	20	32.3%
≥ 80 years	5	8.1%
Total	62	100.0%

The second variable in our investigation was sex, with males comprising over three-quarters of the patients (77.4%) and females accounting for less than one-quarter (22.6%), as reported in Table 2.

Table 2: Distribution of patients with non-small carcinoma according to sex (N=62).

Sex	Number	%
Male	48	77.4%
Female	14	22.6%
Total	62	100.0%

Tumors are classified based on their grade which reflects their resemblance to the original normal tissue (WHO grading system). As shown in Table 3, histopathological examination of H and E slides from our study showed that twenty patients (32.3%) had well-differentiated carcinoma, twenty-five patients (40.3%) had moderately differentiated carcinoma, and seventeen patients (27.4%) had poorly differentiated carcinoma.

Table 3: Distribution of patients with non-small carcinoma according to grade of tumor (N=62)

Grade of tumor	Number	%
Well differentiated	20	32.3%
Moderately differentiated	25	40.3%
Poorly differentiated	17	27.4%
Total	62	100.0%

The average age difference of patients with non-small cell carcinoma in our study based on programmed death-ligand 1 (PD-L1) positivity. Patients with positive PD-L1 exhibited a notable mean age elevation (67.52 ± 9.46 years) compared to those with a negative result (60.71 ± 11.67 years), with a P value of 0.016, as stated in Table 4.

Table 4: The mean difference of age of patients with non-small cell carcinoma according to Programmed death-ligand 1 staining (N=62)

Study variable	Programmed death-ligand 1 (PD-L1)		Total (N=62)	P-value
	Positive (N=27)	Negative (N=35)		
Age (years)	(67.52 ± 9.46)	(60.71 ± 11.67)	(63.68 ± 11.21)	**0.016***

Our variables, apart from age, are integrated with Programmed Death-Ligand 1 (PD-L1) expression as recorded in Table 5. A substantial correlation existed between programmed death ligand 1 (PD-L1) and tumor grade. Well-differentiated carcinoma was observed at a higher prevalence in patients with negative PD-L1 compared to those with positive PD-L1. Among patients with negative PD-L1, fewer than half (N = 17, 48.6%) had well-differentiated carcinoma, whereas only 3 patients (11.1%) with positive PD-L1 displayed well-differentiated carcinoma. There is no correlation between sex and tumor types.

Table 5: The association between Programmed death-ligand 1 (PD-L1) staining and study variables (N=62)

Study variables	Programmed death-ligand 1 (PD-L1)		Total (N=62)	P-value
	Positive (N=27)	Negative (N=35)		
Sex of patient				
Male	19 (70.4)	29 (82.9)	48 (77.4)	0.244
Female	8 (29.6)	6 (17.1)	14 (22.6)	
Total	27 (100.0)	35 (100.0)	62 (100.0)	
Grade of tumor				
Well differentiated	3 (11.1)	17 (48.6)	20 (32.3)	
Moderately differentiated	16 (59.3)	9 (25.7)	25 (40.3)	**0.004***
Poorly differentiated	8 (29.6)	9 (25.7)	17 (27.4)	
Total	27 (100.0)	35 (100.0)	62 (100.0)	
Type				
Squamous cell	13 (48.1)	17 (48.6)	30 (48.4)	
carcinoma	14 (51.9)	18 (51.4)	32 (51.6)	0.974
Adenocarcinoma	27 (100.0)	35 (100.0)	62 (100.0)	
Total				

Programmed death-ligand 1 (PD-L1) and squamous cell carcinoma grade are related. Well-differentiated cancer was observed at a greater frequency in individuals with negative PD-L1 compared to those with positive PD-L1. Fewer than half of the patients who tested negative for PD-L1 (N = 7) had well-differentiated carcinoma, while all of the patients who tested positive for PD-L1 (100% of them) had either moderately differentiated or poorly differentiated carcinoma. This is a significant correlation with a P value of 0.02, as shown in Table 6.

Table 6: The association between (PD-L1) staining and grade of tumor among patients with Squamous cell carcinoma (N=30)

Grade of tumor	Programmed death-ligand 1 (PD-L1)		Total (N=30)	P-value
	Positive (N=13)	Negative (N=17)		
Well differentiated	0 (0.0)	7 (41.2)	7 (23.3)	**0.02***
Moderately differentiated	8 (61.5)	5 (29.4)	13 (43.4)	
Poorly differentiated	5 (38.5)	5 (29.4)	10 (33.3)	
Total	13 (100.0)	17 (100.0)	30 (100.0)	

Table 7 illustrate the positive results of Programmed Death-Ligand 1 (PD-L1) in various grades of adenocarcinoma patients, revealing no significant link with a P value of 0.09.

Table 7: The association between (PD-L1) staining and grade of tumor among patients with Adenocarcinoma (N=32).

Grade of tumor	Programmed death-ligand 1 (PD-L1)		Total (N=32)	P-value
	Positive (N=14)	Negative (N=18)		
Well differentiated	3 (21.4)	10 (55.6)	13 (40.6)	0.09
Moderately differentiated	8 (57.2)	4 (22.2)	12 (37.5)	
Poorly differentiated	3 (21.4)	4 (22.2)	7 (21.9)	
Total	14 (100.0)	18 (100.0)	32 (100.0)	

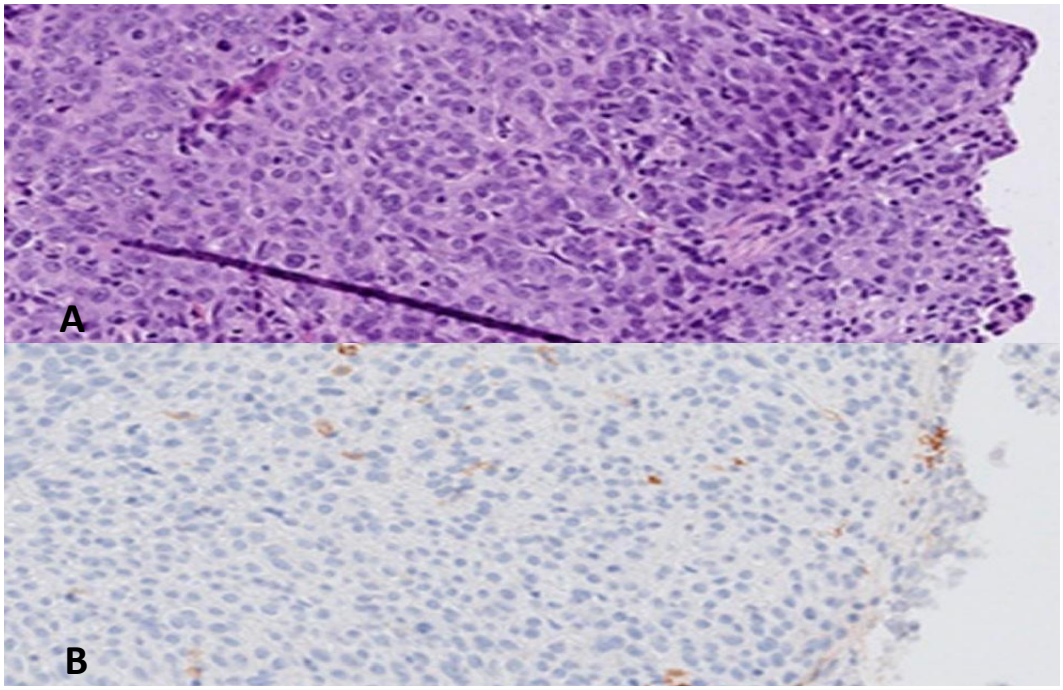

Figure 1: Squamous cell carcinoma in H&E (A) with negative PDL1 staining (B).

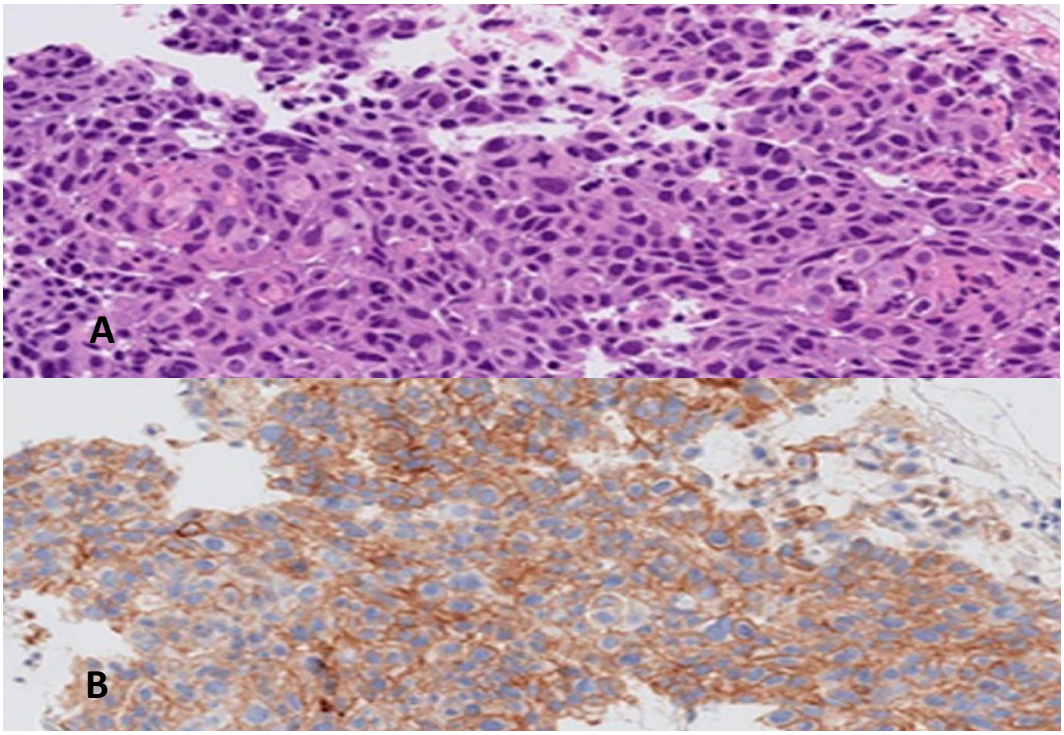

Figure 2: Squamous cell carcinoma by H&E (A) with positive PDL1 stain and high expression > 50% (B).

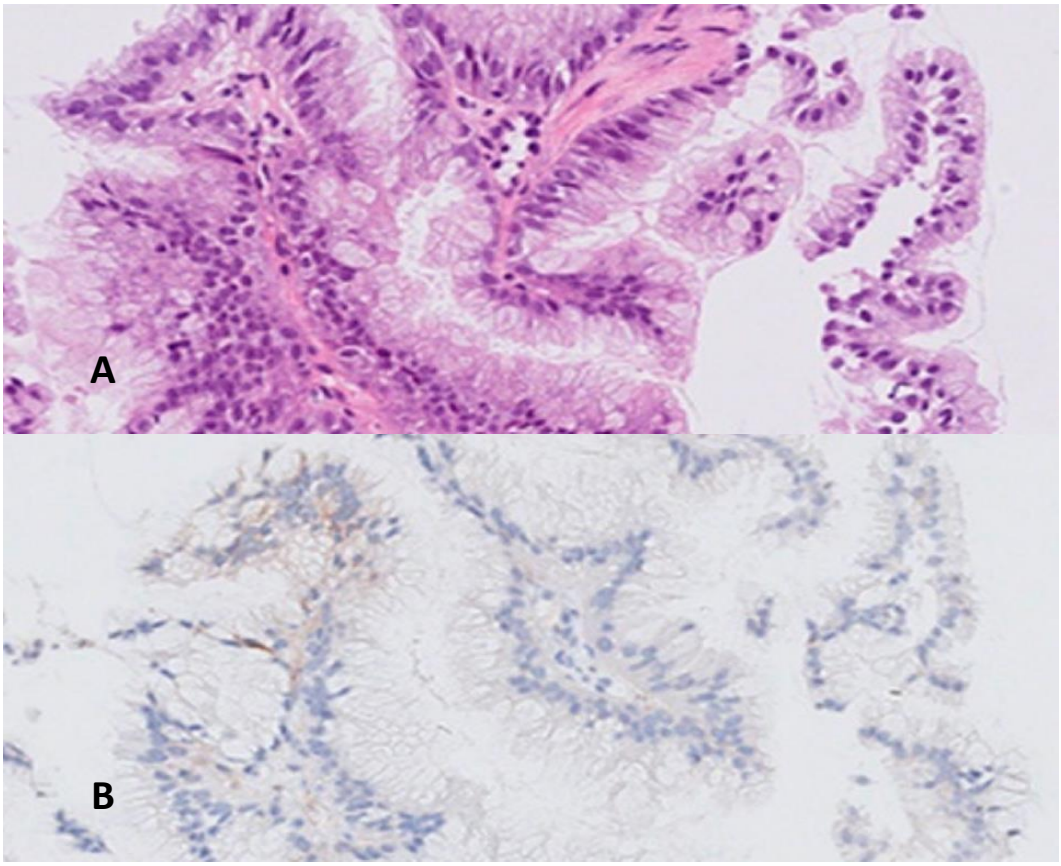

Figure 3: Adenocarcinoma by H&E (A) and negative PDL1 stain (B).

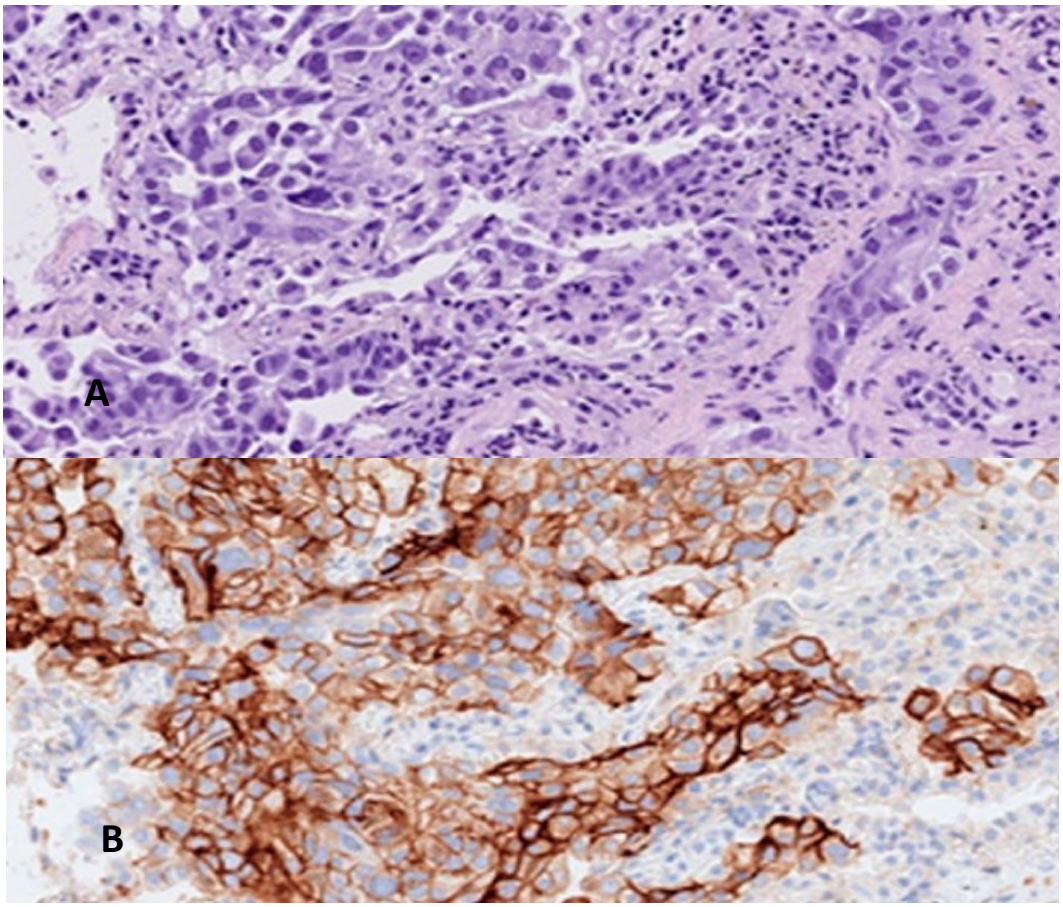

Figure 4: Adenocarcinoma by H &E (A) with positive PDL1 stain and high expression >50% (B).

DISCUSSION

One of the several immune evasion strategies used by lung tumours is the elevation of PD-L1 expression in response to persistent T cell receptor activation. Oncogenic signals and inflammatory cytokines stimulate PD-L1, which compromises T cell function, lowers cytokine generation, and increases tumour survival.[7] Reviewing 62 instances of non-small cell lung cancer (NSCLC), graded per WHO classification, with immunohistochemical examination of PD-L1 expression in association with age, gender, tumour type, and tumour grade, this study with an overall PD-L1 positive rate of 43.5%, NSCLC's[8] recorded expression range of 13%–75% fits exactly. These results match those of Manish Kumar et al. (33.6%)[9], Dhawan et al. (44%)[10], and Saif et al. (40%).[11] With regard to age, patients fell between 31 and 85 years. Older age and positive PD-L1 expression (mean age 67.52 ± 9.46, p = 0.016) showed a clear connection. This fits well established biological processes like cumulative carcinogenic exposure, chronic inflammation, and aging-related immune dysregulation. Our results probably reflect more thorough age stratification in our study than those of Manish Kumar et al.[9], Saez de Gordoa et al.[12], and Saif et al.[11] No significant association was found between PD-L1 expression and gender (p = 0.244), supporting the findings of Saez de Gordoa et al.[12] but differing from Manish Kumar et al.[68], who noted a male predominance possibly due to environmental exposures. Analysis of tumor grade showed a significant association with PD-L1 expression: only 3/20 well-differentiated cases were positive, while 16/25 moderately and 8/17 poorly differentiated cases were positive. This supports the hypothesis that dedifferentiation correlates with increased PD-L1 expression due to enhanced mutational burden, inflammation, cytokine (e.g., IFN) induction, and immune evasion. Our findings agree with Manish Kumar et al.[9], Kojima et al.[13], and Saif et al.[11] While no significant correlation was found between the level of PD-L1 expression and demographic or tumor type variables overall, significance emerged when stratified by tumor type. In adenocarcinoma cases, low expressors (TPS <50%) were mostly moderately differentiated, while high expressors (TPS ≥50%) were poorly differentiated (p = 0.027). This aligns with García et al.[14], who observed high TPS in poorly differentiated adenocarcinomas, and Pan et al.[15], who found significant expression in solid subtype ADC. Saif et al.[11] also reported strong associations between PD-L1 expression and solid adenocarcinoma subtype (p = 0.004). This single-center study had a limited sample size and included only small biopsy specimens, potentially overlooking tumor heterogeneity. Surgical specimens were not examined, and tumor staging was not assessed. Additionally, PD-L1 expression was not correlated with treatment response or prognosis. Further multi-center studies are needed.

CONCLUSION

PD-L1 expression was significantly observed in NSCLC cases and was strongly associated with poorer differentiation. A significant correlation was found with older age, while no association was seen with gender or tumor histological subtype (SCC vs. adenocarcinoma).

REFERENCES

1. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non- small-cell lung cancer. N Engl J Med., Jan. 2002; 346(2): 92–8.
2. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Path. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer, Jul. 2013; 8(7): 823–59.
3. Ribas A. Releasing the Brakes on Cancer Immunotherapy. N Engl J Med., Oct. 2015; 373(16): 1490–2.
4. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw, May 2022; 20(5): 497–530.
5. Kerr KM, Tsao MS, Nicholson AG, Yatabe Y, Wistuba II, Hirsch FR. Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer: In what state is this art? J Thorac Oncol Off Publ Int Assoc Study Lung Cancer, Jul. 2015; 10(7): 985–9.
6. Zhang M, Li G, Wang Y, Wang Y, Zhao S, Haihong P, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. Sci Rep., Aug. 2017; 7(1): 10255.
7. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol, Feb. 2016; 39(1): 98–106.
8. Jain P, Kumar Chauhan N, Chakraborti A, Gupta MK, Dutt N, Jalandra RN, et al. Programmed cell death ligand 1 (PD-L1) expression in non-small cell lung cancer: Findings from a tertiary care institute in western part of India. Indian J Tuberc [Internet], 2023; 70(4): 416–21. Available from: https://doi.org/10.1016/j.ijtb.2023.01.001
9. Manish Kumar, Bhupesh Guleria, Shivashankar Swamy, Sneha Soni. Correlation of programmed death‐ligand 1 expression with gene expression and clinicopathological parameters in Indian patients with non‐small cell lung cancer. Lung India [Internet], 2018; 35(1): 41–6. Available from: https://pubmed.ncbi.nlm.nih.gov/32367847/
10. Dhawan V, Chandra S, Kala M, Khanduri S. Expression of PD-L1 in Lung Carcinoma and Its Correlation with Histopathological Grade, Stage,

and Survival of Patients. J Lab Physicians, 2023; 15(02): 289– 93.
11. Saif H, Kumar KSR, Mufti SS, Giri R, Hrishi V, Sarathy V, et al. Correlation of Programmed Death Ligand-1 (PD-L1) Expression with Clinicopathological Features in Non-Small Cell Lung Carcinoma: Experience from a Tertiary Cancer Care Center in India. J Cancer Ther., 2020; 11(03): 172–87.
12. Saez de Gordoa K, Lopez I, Marginet M, Coloma B, Frigola G, Vega N, et al. Pd-l1 expression in non-small cell lung cancer: Data from a referral center in Spain. Diagnostics, 2021; 11(8): 1–12.
13. Kojima K, Sakamoto T, Kasai T, Atagi S, Yoon H. A quantitative evaluation of the histological type dependence of the programmed death-ligand 1 expression in non-small cell lung cancer including various adenocarcinoma subtypes: A cross-sectional study. Jpn J Clin Oncol, 2022; 52(3): 281–5.
14. García A, Recondo G, Greco M, de la Vega M, Perazzo F, Avagnina A, et al. Correlation between PD-L1 expression (clones 28-8 and SP263) and histopathology in lung adenocarcinoma. Heliyon, 2020; 6(6): 4–7.
15. Pan Y, Zheng D, Li Y, Cai X, Zheng Z, Jin Y, et al. Unique distribution of programmed death ligand 1 (PD-L1) expression in East Asian non-small cell lung cancer. J Thorac Dis., August 28, 2017; 9(8). J Thorac Dis [Internet]. 2017; Available from: https://jtd.amegroups.org/article/view/15037.