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Original Article

Pathology Section

PD-L1 Expression in Cervical Intraepithelial Neoplasia and Carcinoma: A Cross-sectional Observational Study

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ABSTRACT

Introduction: Programmed Death-Ligand 1 (PD-L1) contributes to immune escape in cervical lesions and may have clinical relevance for risk stratification and immunotherapy. The present study addresses the need for a uniform revaluation of PD-L1 expression across the pre-invasive to invasive cervical neoplasia spectrum using a combined intensity-and-proportion scoring approach.

Aim: To evaluate PD-L1 expression in Cervical Intraepithelial Neoplasia (CIN) and invasive carcinoma using a predefined, uniform immunohistochemical scoring protocol.

Material and Methods: The present cross-sectional observational study was conducted at Meenakshi Medical College Hospital and Research Institute, Kanchipuram, Tamil Nadu, India. from May 2024 to December 2025. Sixty cervical biopsy specimens were analysed, comprising 10 cases each of CIN-1, CIN-2 and CIN-3, and 30 cases of invasive carcinoma. PD-L1 staining intensity and the proportion of positive lesion cells were scored from 0 to 3, and a composite score (0-6) was obtained by adding the two scores. Expression was categorised as negative (0), low (1-2), intermediate (3) or strong (4-6). Data were analysed using Statistical Package for Social Sciences (SPSS) version 26.0 with Pearson's chi-square tests, Cochran-Armitage trend tests, Kruskal-Wallis tests, Mann-Whitney U-tests and multivariable binary logistic regression.

Results: The study included 60 cases; based on grouped age mid-points, the estimated mean age was 43.5 years. Overall, 21/60 (35%) cases were PD-L1 positive. Positivity was 0/10 (0%) in CIN-1, 3/10 (30.0%) in CIN-2, 5/10 (50.0%) in CIN-3 and 13/30 (43.3%) in invasive carcinoma. The association between diagnosis and PD-L1 positivity approached significance (Pearson's chi-square=7.40, p=0.060), while a significant increasing trend was observed across CIN grades (Cochran-Armitage-Z=2.53, p=0.011). PD-L1 positivity also differed across age groups (chi-square=8.71, p=0.033), with a significant age-related trend (Z=2.70, p=0.005). Multivariable logistic regression showed that each one-level increase in diagnostic severity was associated with higher odds of PD-L1 positivity (Odds Ratio (OR)=1.91; 95% Confidence Interval (CI): 1.07-3.41; p=0.029). Composite scores differed significantly across diagnostic categories (Kruskal-Wallis H=8.32, p=0.040).

Conclusion: PD-L1 expression increased from low-grade to high-grade CIN and remained frequent in invasive carcinoma. These findings support the role of PD-L1 as an immune related biomarker in cervical neoplasia and justify further evaluation of standardised PD-L1 assessment for risk stratification and treatment planning.

Keywords: Biomarkers, Composite scoring, Immune invasion, Immunohistochemistry, Precancerous lesions,Programmed death-ligand 1, Squamous cell carcinoma

INTRODUCTION

Cervical cancer remains a major global health burden, especially its prevalence is quite prominent across the lower and middle income nations, despite the widespread awareness and diagnostic progress like cytology-screening followed by the increased administration of prophylactic Human Papillomavirus (HPV) vaccinations [1,2]. Persistent infection with High-Risk HPV (HR-HPV), especially types 18 and 16, is considered as the central etiologic factor responsible for cervical carcinogenesis, which serves as well-characterised multistep progression from CIN to invasive carcinoma via deregulating epithelial differentiation followed by the accumulation of epigenetic and genetic alterations within the affected individuals [3,4]. Although majority of the HPV cases regress spontaneously, the subset persists and progresses, thus reflecting the lack of local cell-mediated immune control mechanism. Understanding how HPV-related lesions evades host immunity system can be therefore crucial in improving risk stratification and identification of candidates for immunotherapy treatment.

One major significance concerning the immune escape mechanisms in HPV-related disease is the activation of the PD-1/PD-L1 axis. PD-1 is an inhibitory receptor expressed on activated T cells, whilst the PD-L1 is expressed on antigen-presenting cells and are further then induced on tumour and epithelial cells in response for the inflammatory cytokines like interferon-γ [3,4]. Engagement of PD-1 by PD-L1 transmits negative signal that attenuates proliferation of T-cell, subsequent production of cytokines, and cytotoxic functioning, thereby facilitating in the promotion of T-cell exhaustion and immune tolerance in the setting of cancer or chronic viral infections [3]. In cervical neoplasia, upregulation of PD-1 on T cells and PD-L1 on dendritic cells and lesional epithelial cells correlates with HR-HPV positivity, increasing CIN grade, and a shift from T helper type 1 to an immunosuppressive cytokine milieu, implicating this pathway in lesion persistence and progression [3].

Immunohistochemical studies have demonstrated that normal cervical epithelium lacks PD-L1 expression, whereas PD-L1 is markedly upregulated in CIN and invasive Squamous Cell Carcinoma (SCC). While Mezache L et al., reported exceptionally high PD-L1 positivity, demonstrating expression in 95% of CIN and 80% of cervical SCC cases [5]. Similar observations regarding elevated PD-L1 expression in cervical lesions have also been discussed

in a systematic review [6]. From such evidences from recent findings representing notably higher than typical observations in recent studies, this discrepancy underscores the critical need for standardised evaluation methodologies. In addition, it is evident that the expression of both PD-L1 and PD-1 increased with CIN grade and HPV positivity, accompanied by decreased interferon-γ and interleukin-12 and increased interleukin-10, indicating impaired local cell-mediated immunity in high-grade lesions [3,7]. In invasive cervical carcinoma, multiple cohorts have reported PD-L1 expression in approximately one-third to two-thirds of cases, with positivity rates of around 31-35% in large series using standardised assays and scoring systems [1,8,9], and up to 57-67% in other observational studies [2,10].

Clinically, the PD-1/PD-L1 axis has become directly relevant because immune-checkpoint inhibitors targeting this pathway have shown activity in advanced and recurrent cervical cancer. Anti-PD-1 agents such as pembrolizumab and nivolumab, and anti-PD-L1 agents, have received regulatory approval for PD-L1-positive cervical carcinoma, typically defined by a Tumour Proportion Score (TPS) or Combined Positive Score (CPS) above an established threshold [4,11]. In this context, PD-L1 Immunohistochemistry (IHC) has been adopted as a predictive biomarker to select patients for therapy. However, the literature is heterogeneous with respect to antibodies, platforms, cut-offs, and scoring methods used for PD-L1 assessment, resulting in wide variability in reported prevalence (~20-95%) and inconsistent associations with clinicopathological parameters and outcomes [1]. Recent work has underscored marked spatial heterogeneity of PD-L1 expression within tumours and highlighted discordance between different assays and scoring algorithms, further complicating standardisation [12].

While PD-L1 expression in invasive cervical carcinoma has been relatively well studied, its dynamics across the full spectrum of pre-invasive disease- particularly ordered trends from CIN-1 through CIN-3- are less clearly defined. Systematic reviews indicate that PD-L1 expression increases from low-grade to high-grade lesions and carcinoma, and is linked to lesion persistence [3,7]. However, individual studies have used disparate scoring systems without integrating staining intensity, potentially underestimating biologically relevant gradations [4,6,13]. Only a minority of series have evaluated PD-L1 across multiple CIN grades and carcinoma within the same cohort. Age and other host factors may further modulate the tumour immune microenvironment, although these relationships often lose significance in multivariable models [2,8,9].

The study addresses existing gaps by systematically quantifying PD-L1 immunoexpressionin cervical biopsy specimens spanning CIN-1 through invasive carcinoma, utilising a reproducible composite scoring system that integrates both staining intensity and positive cell proportion. By formally testing for ordered trends according to lesion grade and age, aiming to clarify whether PD-L1 expression increases progressively along the neoplastic continuum, providing a rationale for its further investigation as a biomarker for risk stratification and immunotherapy.

MATERIALS AND METHODS

The present cross-sectional observational research of PD-L1 expression in CIN and invasive cervical carcinoma was conducted at Meenakshi Medical College Hospital and Research Institute, Kanchipuram, Tamil Nadu, India, from May 2024 to December 2025. Ethical approval was obtained from the Institutional Ethics Committee (MMCH&RI/PG/10/MAY/24).

Sample size calculation: To calculate sample size, n=Z2 P(1-P)/d2 was used where Z=1.96 is for 95% confidence level, P=0.35 from previously reported PD-L1 prevalence in cervical carcinoma [8], d=0.12 is allowable absolute precision. The result of this calculation was approximately 61 cases to be included with 60 available eligible cases. Cases were purposefully chosen so that there were representatives of all four groups (CIN-1, CIN-2, CIN-3 and those with invasive carcinoma)

Inclusion and Exclusion criteria: Formalin-fixed, paraffin-embedded cervical biopsy specimens obtained for routine diagnostic purposes were included when adequate lesional epithelium and preserved tissue architecture were present. Poorly preserved, inadequately fixed or insufficient biopsies were excluded.

Study Procedure

Age at diagnosis was categorised into four groups: <35, 35-44, 45-54 and >55 years.

Immunohistochemistry (IHC) and PD-L1 scoring: Evaluation of PD-L1 protein expression was done using IHC on 4 µm tissue sections. Following the deparaffinisation and heat-induced epitope retrieval, the sections were incubated with primary anti-PD-L1 rabbit monoclonal antibody (Path in situ, dilution 1:100). Detection was performed using secondary antibody and peroxidase-based visualisation system with 3,3′-Diaminobenzidine (DAB) as chromogen, followed by haematoxylin counterstaining.

Assessment of PD-L1 staining assessed for the lesional epithelial/tumour cells by employing semi-quantitative scoring system which was adapted from the previously reported approaches on the CIN and cervical carcinoma [14]. Two parameters were evaluated for each case:

i. Staining intensity of the membranous and/or cytoplasmic PD-L1 expression in lesional cells, scored on a 4-point scale:

- 0=No staining
- 1=Weak staining
- 2=Moderate staining
- 3=Strong staining

ii. Proportion of positive lesional cells, scored according to estimated percentage of PD-L1-positive cells within the lesional epithelium:

- 0=0% positive cells
- 1=1-10% positive cells
- 2=11-50% positive cells
- 3=>50% positive cells

A composite PD-L1 score ranging from 0-6 was determined by summing proportion and intensity scores. On the basis of composite score achieved, PD-L1 expression was categorised as negative (0), low expression (1-2), intermediate expression (3), and strong expression (4-6) [14]. For binary analysis, any composite score greater than zero was considered PD-L1 positive. All slides were independently evaluated by experienced pathologists who were blinded to clinical information. Cases with discrepant interpretations were jointly reviewed to achieve consensus before final reporting.

STATISTICAL ANALYSIS

Data were analysed using version 26.0 of SPSS statistical software. Categorial variables were summarised as frequencies (e.g., number of patients) or percentages of total sample size. The estimated mean age was calculated using a midpoint weighted method, by multiplying the frequency in each age group by the midpoint of that age group, summing these values across all age groups, and dividing by the total number of cases. Categorical variable relationships were analysed with Pearson's chi-square testing, and ordered trending data comparisons were made with Cochran-Armitage testing. Multivariable analysis applying binary logistic regression was used to evaluate PD-L1 positive versus diagnosis severityand age group was estimated using Odds Ratios (OR) with 95% CIs. Composite score distribution analyses were performed with a Kruskali-Wallis test and a Mann-Whitney U-Test. A significance level of p-value less than 0.05 was used throughout these analyses.

RESULTS

PD-L1 positivity and distribution by diagnosis: The analysed group had 60 cervical biopsy specimens with, 10 CIN-1, 10 CIN-2, 10 CIN-3, and 30 invasive carcinoma cases [Table/Fig-1]. For the ages it was <35 years in 11 cases, 35-44 years in 21 cases, 45-54 years in 22 cases, and >=55 years in 6 cases. While using the midpoint-based estimate, the mean age came out to 43.5 years.

PD-L1 positivity was positive in 21/60 (35%) cases. No cases of PD-L1 positivity were present in CIN-1 0/10 (0%). PD-L1 positivity occurred in 3/10 (30%) of CIN-2 and was found to be the highest percentage of PD-L1 positivity among CIN-3 5/10 (50%). The percentage of PD-L1 positivity in invasive carcinoma was 13/30 (43.3%). The strongest expression of PD-L1 was found in the CIN-3 and invasive carcinoma groups.

Diagnosis	n	PD-L1 negative n (%)	PD-L1 positive n (%)	PD-L1 composite-score category among positive cases
CIN-1	10	10 (100.0)	0	Low 0, Intermediate 0, Strong 0
CIN-2	10	7 (70.0)	3 (30.0)	Low 2, Intermediate 1, Strong 0
CIN-3	10	5 (50.0)	5 (50.0)	Low 0, Intermediate 1, Strong 4
Carcinoma	30	17 (56.7)	13 (43.3)	Low 2, Intermediate 6, Strong 5
Total	60	39 (65.0)	21 (35.0)	

[Table/Fig-1]: PD-L1 positivity and composite-score category by diagnosis (n=60) Pearson's chi-square=7.40, df=3, p=0.060; Cochran-Armitage trend across CIN grades: Z=2.53, p=0.011; Kruskal-Wallis test for composite scores across diagnostic categories: H=8.32, p=0.040.

Association of PD-L1 positivity with age group: [Table/Fig-2] showed that the PD-L1 positivity gradually increases with the higher age group. In the age group with participants <35-years, there were 0/11 (0%) cases; for the 35-44-year group it was 7/21 (33.3%) cases. Then for 45-54-year it became 11/22 (50%) cases, and in the >=55-year group it also sat at 3/6 (50%) cases.

Age group	n	PD-L1 positive, n (%)	PD-L1 negative, n (%)
Less than 35 years	11	0	11 (100.0%)
35-44 years	21	7 (33.3%)	14 (66.7%)
45-54 years	22	11 (50.0%)	11 (50.0%)
Above 55 years	6	3 (50.0%)	3 (50.0%)

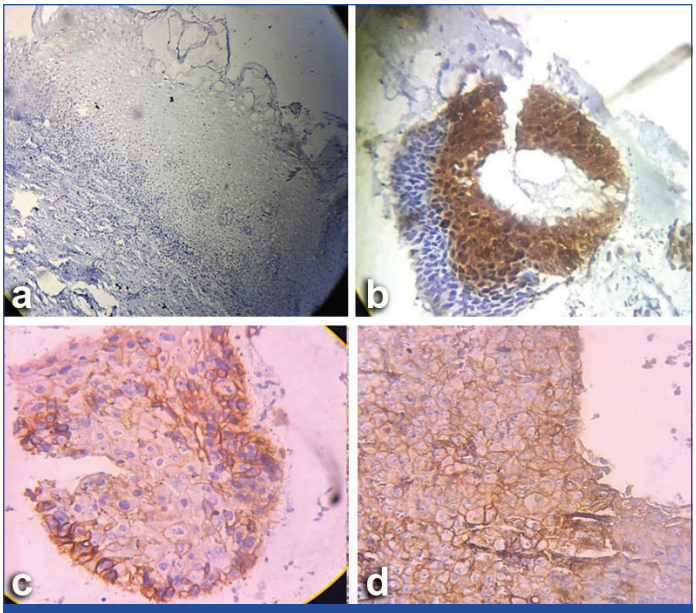
[Table/Fig-2]: PD-L1 positivity by age group (n=60). Pearson's chi-square=8.71, df=3, p=0.033; age-related Cochran-Armitage trend: Z=2.70, p=0.005

Multivariable modelling of PD-L1 positivity: [Table/Fig-3] presented the multivariable binary logistic regression, wherein the diagnostic severity was significantly associated with PD-L1 positivity (OR=1.91, 95% CI: 1.07-3.41, p=0.029). Age group showed higher odds with increasing category but not statistically significant after adjustment (OR=1.53, 95% CI: 0.84-2.80, p=0.163).

Predictor	OR	95% CI	p-value
Diagnosis severity (per one-level increase)	1.91	1.07-3.41	0.029
Age group (per one-category increase)	1.53	0.84-2.80	0.163

[Table/Fig-3]: Multivariable binary logistic regression predicting PD-L1 positivity (n=60).

Histomorphological features on H&E examination: The images below represent the pattern of staining over the various classifications used to make a diagnosis. For example, within the category of CIN-1, the staining is absent. The staining is focally present in some areas for CIN-2, widespread for all areas of CIN-3 and moderate to strong positivity for SCC (invasive) [Table/Fig-4a-d].



[Table/Fig-4]: Representative PD-L1 Immunohistochemistry (IHC) in cervical lesions: a) CIN-1 showing absence of membranous staining (IHC 10X); b) CIN-2 showing focal membranous positivity (IHC, 10x); c) CIN-3 showing diffuse. membranous positivity (IHC, 10x); d) Invasive Squamous Cell Carcinoma (SCC). Showing moderate membranous positivity in tumour nests.(IHC, 10x).

DISCUSSION

The present study demonstrates that PD-L1 expression in cervical neoplasia is uncommon in low-grade lesions but becomes progressively more frequent and more intense with increasing histological severity, supporting an immunobiologic model in which immune checkpoint activation accompanies lesion progression. PD-L1 positivity was absent in CIN-1, present in 30% of CIN-2 and 50% of CIN-3, and remained common in invasive carcinoma (43.3%). Strong PD-L1 expression (composite score 4-6) was confined to CIN-3 and carcinoma, whereas CIN-1 and CIN-2 showed only low or intermediate expression. Although the overall association between diagnosis and PD-L1 positivity narrowly missed conventional statistical significance in univariable analysis (χ^2 p=0.060), multivariable modelling confirmed that each stepwise increase in diagnostic severity (from CIN-1 to carcinoma) nearly doubled the odds of PD-L1 positivity (OR 1.91, 95% CI 1.07-3.41, p=0.029). These findings are consistent with the concept that PD-L1 upregulation is linked to biologic progression along the CIN-carcinoma continuum.

The direction of these results aligns with several prior studies showing an increase in PD-L1 expression with CIN grade and into invasive cancer. Yang W et al., reported that PD-L1 and PD-1 expression on cervical immune cells rose in parallel with CIN grade and HR HPV positivity [15], accompanied by a shift toward an immunosuppressive cytokine milieu, indicating that the PD-1/PD-L1 pathway contributes to impaired local cell-mediated immunity in HR-HPV-related CIN [15]. A recent systematic review [6] similarly concluded that PD-L1 expression in both cervical epithelial and mononuclear cells increase from Low-grade Squamous Intraepithelial Lesion (LSIL)/CIN-1 through High-grade Squamous Intraepithelial Lesion (HSIL)/CIN2+ to carcinoma, supporting a role for PD-L1 in lesion persistence and progression [16]. As discussed earlier by with higher PD-L1 expression in cases with CIN-1/2 lesions (95%) and also among squamous carcinomas cases (80%), with expression localised to dysplastic/neoplastic cells and $CD8^+$ lymphocytes [5]. This evidently showcases the role of PD-L1 as a potential biomarker for diagnosis against HPV infection. The absolute prevalence of PD-L1 positivity in the present series (particularly the absence in CIN-1) is lower than in some of these reports, likely reflecting differences in antibody clones, scoring systems, and cut-offs [11,17]. However, the key biological signal- a stepwise increase in expression with histologic severity and restriction of strong expression to high-grade and invasive disease- is concordant with the broader literature [4,18].

The age-stratified analysis showed a significant increase in PD-L1 positivity with advancing age, from 0% under 35 years to 50% in both the 45-54 and ≥55-year groups (p=0.033). This monotonic pattern suggests that the probability of encountering PD-L1-expressing

lesions increases with age, potentially reflecting age-related immune senescence or accumulated exposure to HR-HPV and other immunomodulatory influences. Similar age-associated trends have been observed in larger carcinoma cohorts [1,8,19]. An Indian cross-sectional study of 119 cervical cancers reported PD-L1 positivity in 35% overall, with higher positivity among women older than 45 years, and other series have noted higher PD-L1 expression in older or more advanced patients, although age is not consistently an independent predictor after adjustment for tumour factors [1,20,21]. In the present study, the independent effect of age did not reach statistical significance in multivariable logistic regression (OR 1.53, 95% CI 0.84-2.80, p=0.163), indicating that histological severity is a more robust determinant of PD-L1 status than age once diagnostic grade is accounted for. This is consistent with meta-analytic data in invasive cervical cancer, where PD-L1 overexpression shows strong associations with adverse survival but not with the patient's age [8,9].

Taken together, these findings reinforce the view that disease biology- specifically progression from low-grade CIN to HSIL and carcinoma- is the primary driver of PD-L1 upregulation in cervical neoplasia. The emergence of strong PD-L1 expression only in CIN-3 and carcinoma suggests that immune evasion via the PD-1/PD-L1 axis is most pronounced at the high-grade pre-invasive and invasive stages, in line with studies reporting progressive increases in PD-L1 and related immune-escape markers from low-grade lesions to cervical SCC [14,22]. This has important implications for immunotherapy: a substantial subset of high-grade CIN and invasive tumours may be biologically primed to respond to PD-1/PD-L1 blockade, as reflected in clinical trials and approvals of PD-1 inhibitors for PD-L1-positive recurrent/metastatic cervical cancer [11,23].

At the same time, the lower PD-L1 prevalence in this cohort compared with some reports (e.g., 31-41% vs ~58-70% in several carcinoma series) [7,24] highlights ongoing challenges in standardising PD-L1 testing. Heterogeneity in antibody clones, platforms, scoring systems (TPS, CPS, or composite scores), and cut-offs yields wide variability in reported positivity rates [4]. Also, there is a marked intratumoural heterogeneity and discordance between PD-L1 IHC cores from the same patient, and proposed RNA-based methods combined with interferon-γ signalling as more robust biomarkers [20]. A large meta-analysis across gynaecologic cancers also showed that pooled PD-L1 prevalence and prognostic impact vary substantially with assay and scoring criteria [9]. The composite intensity-plus-proportion score used in this study is conceptually similar to H-score-type approaches and captures gradations in expression, but cross-study comparisons must be interpreted cautiously.

Limitation(s)

There are several limitations that warrant consideration. The sample size within each CIN subgroup was modest, contributing to borderline p-values in univariable analyses and limiting power to explore interactions between age, HPV status, and PD-L1 expression. The cross-sectional design precludes conclusions about temporal dynamics or causality and does not allow assessment of prognostic implications or treatment response. HPV genotyping, immune-cell PD-L1 and PD-1 expression, and other microenvironmental markers (e.g., $CD8^+$ TILs, cytokines) were not evaluated, although prior work indicates that PD-L1/PD-1 status, TIL density, and cytokine profiles jointly shape prognosis and response to immunotherapy. Finally, as emphasised in recent reviews and regulatory analyses, PD-L1 alone is an imperfect predictive biomarker for checkpoint blockade, with only a subset of PD-L1-positive cancers responding and some PD-L1-negative tumours deriving benefit. Also, HPV genotyping and viral load quantification were not performed, so the relationship between specific HR HPV types, and PD-L1 status could not be directly evaluated.

Future research should build on these findings through larger, multicentred, and preferably prospective cohorts that include all grades of CIN and invasive carcinoma, with long-term clinical follow-up. Such studies should correlate PD-L1 expression with HPV genotype, viral load, and molecular signatures to clarify the pathways linking transforming HPV infection to immune checkpoint activation. Integrating standardised, guideline-concordant PD-L1 assays and scoring systems, along with detailed characterisation of the tumour immune microenvironment (including PD-1/PD-L1 expression on immune cells, $CD8^+$ T-cell infiltration, and other checkpoints such as CTLA-4, LAG-3, and TIM-3), would help refine biomarker panels for predicting progression and therapeutic response. In invasive carcinoma, translational studies linking PD-L1 profiles to response rates and survival in patients treated with immune-checkpoint inhibitors could support personalised immunotherapy strategies. Finally, exploratory work combining PD-L1 with other emerging markers (e.g., tumour mutational burden, gene expression profiles, spatial immune mapping) may lead to robust, multiparametric models for risk stratification and treatment selection across the spectrum of HPV-related cervical disease.

CONCLUSION(S)

The present cross-sectional analysis of 60 cervical biopsy specimens demonstrates that immune-related biomarkers, particularly PD-L1, are closely linked to the histological progression of cervical disease. PD-L1 expression was absent in low-grade lesions (CIN-1), emerged in a subset of CIN-2, and became frequent in CIN-3 and invasive carcinoma, with significant evidence of an increasing trend across CIN grades. Although an age-related trend was noted in univariable analysis, the loss of its independent statistical significance in multivariable modeling highlights that PD-L1 upregulation is primarily driven by the underlying biological severity of the lesions. Collectively, these findings support a model in which the transforming HPV infections and PD-L1- mediated immune evasions tend to co-evolve during the cervical carcinogenesis. Clinically, this underscores the potential of PD-L1 as an adjunct biomarker for risk stratification in high-grade CIN and carcinoma cases, and could serve as a rational target for immune-checkpoint-mediated therapies in a subset of cervical lesions.

REFERENCES

[1] Anwer MA, Sinha R, Bharti S, Surabhi, Kumar T, Singh A. Clinicopathological association of Programmed Death-Ligand 1 (PD-L1) expression in uterine cervical carcinomas: A cross-sectional observational study. Indian J Pathol Microbiol. 2025;68(3):472-77. Doi: 10.4103/ijpm.ijpm_572_24. Epub 2025 Jun 7. PMID: 40485406.

[2] Baek M, Chen L, Tekin C, Cristescu R, Jin X, Shao C, et al. Prevalence and prognostic value of PD-L1 expression and tumor mutational burden in persistent, recurrent, or metastatic cervical cancer. J Gynecol Oncol. 2024;35:e105. Doi: 10.3802/jgo.2024.35.e105.

[3] Brito M, Sequeira P, Quintas A, Silva I, Silva F, Martins C, et al. Programmed death-ligand 1 (PD-L1) expression in cervical intraepithelial neoplasia and cervical squamous cell carcinoma of HIV-infected and non-infected patients. Virchows Arch. 2023;484:507-16. Doi: 10.1007/s00428-023-03580-z.

[4] Davis A, Patel V. The role of PD-L1 expression as a predictive biomarker: An analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer. 2019;7(1):278. Doi: 10.1186/s40425-019-0768-9.

[5] Mezache L, Paniccia B, Nyinawabera A, Nuovo G. Enhanced expression of PD-L1 in cervical intraepithelial neoplasia and cervical cancers. Mod Pathol. 2015;28:1594-602. Doi: 10.1038/modpathol.2015.108.

[6] Dominoni M, Inzani F, Gritti A, Pasquali M, Mauri M, Eldar A, et al. The role of programmed death-ligand 1 (PDL-1) in high-grade cervical intraepithelial neoplasia (CIN2+) development and recurrence: A systematic review of literature about HPV-CIN2+-PDL-1 axis. Pathol Res Pract. 2024;264:155712. Doi: 10.1016/j.prp.2024.155712.

[7] Enwere E, Kornaga E, Dean M, Koulis T, Phan T, Kalantarian M, et al. Expression of PD-L1 and presence of CD8-positive T cells in pre-treatment specimens of locally advanced cervical cancer. Mod Pathol. 2017;30:577-86. Doi: 10.1038/modpathol.2016.221.

[8] Fu H, Fu Z, Mao M, Si L, Bai J, Wang Q, et al. Prevalence and prognostic role of PD-L1 in patients with gynecological cancers: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2023:104084. Doi: 10.1016/j.critrevonc.2023.104084.

[9] Gu X, Dong M, Liu Z, Mi Y, Yang J, Zhang Z, et al. Elevated PD-L1 expression predicts poor survival outcomes in patients with cervical cancer. Cancer Cell Int. 2019;19:146. Doi: 10.1186/s12935-019-0861-7.

[10] Heeren A, Punt S, Bleeker M, Gaarenstroom K, Velden J, Kenter G, et al. Prognostic effect of different PD-L1 expression patterns in squamous cell carcinoma and adenocarcinoma of the cervix. Mod Pathol. 2016;29:753-63. Doi: 10.1038/modpathol.2016.64.
[11] Huang W, Liu J, Xu K, Chen H, Bian C. PD-1/PD-L1 inhibitors for advanced or metastatic cervical cancer: From bench to bed. Front Oncol. 2022;12:849352. Doi: 10.3389/fonc.2022.849352.
[12] Kaur A, Kaur M, Singh A, Khanna M, Singh K, Khanna I. Clinicopathological correlation and expression of PD-L1 in cervical carcinoma: An immunohistochemical study. J Pathol Nepal. 2024;14(2):2203-08. Doi: 10.3126/jpn.v14i2.65788.
[13] Lathika A, Lakshmi S, Ramdas P, Kumar A, Mathews S, Joseph J, et al. Programmed Death Ligand 1 (PD-L1) expression in cervical cancer. Indian J Gynecol Oncol. 2021;19:01-06. Doi: 10.1007/s40944-021-00584-y.
[14] Meng Y, Liang H, Hu J, Liu S, Hao X, Wong M, et al. PD-L1 Expression correlates with tumor infiltrating lymphocytes and response to neoadjuvant chemotherapy in cervical cancer. J Cancer. 2018;9:2938-45. Doi: 10.7150/jca.22532.
[15] Yang W, Song Y, Lu Y, Sun J, Wang H. Increased expression of programmed death (PD)-1 and its ligand PD-L1 correlates with impaired cell-mediated immunity in high-risk human papillomavirus-related cervical intraepithelial neoplasia. Immunology. 2013;139(4):513-22. Doi: 10.1111/imm.12101.
[16] Omenai S, Ajani M, Okolo C. Programme death ligand 1 expressions as a surrogate for determining immunotherapy in cervical carcinoma patients. PLoS One. 2022;17:e0263615. Doi: 10.1371/journal.pone.0263615.
[17] Petrica L, Deacu M, Cozaru G, Mitroi A, Bălţătescu G, Enciu M, et al. Interplay Between Immune Microenvironment CD8+ Tumor-Infiltrating Lymphocytes and PDL-1 Expression as Prognostic Markers in Invasive Cervical Squamous Cell Carcinoma. Medicina (Kaunas). 2025;61(11):2007. Doi: 10.3390/medicina61112007.
[18] Raju K, Chaudhary N, Sheela S, Sakalecha A, Manjunath G. Programmed death ligand (PD-L1) expression in invasive squamous cell carcinoma of the uterine cervix: A cross-sectional observational study. Cancer Res Stat Treat. 2022;5(3):461-67. Doi: 10.4103/crst.crst_98_22.
[19] Reddy O, Shintaku P, Moatamed N. Programmed death-ligand 1 (PD-L1) is expressed in a significant number of the uterine cervical carcinomas. Diagn Pathol. 2017;12. Doi: 10.1186/s13000-017-0631-6.
[20] Rotman J, Otter L, Bleeker M, Samuels S, Heeren A, Roemer M, et al. PD-L1 and PD-L2 expression in cervical cancer: Regulation and biomarker potential. Front Immunol. 2020;11:596825. Doi: 10.3389/fimmu.2020.596825.
[21] Ruan Y, Xia R, Luo S, Li R, Dong X, Wang J, et al. Upregulation of PD-L1 and MMP9 in HR-HPV-associated cervical squamous cell carcinoma: Correlation with histological progression and immune microenvironment remodeling. Am J Transl Res. 2025;17(10):8364-74. Doi: 10.62347/byvl1679.
[22] Yang W, Lu Y, Yang Y, Kang J, Jin Y, Wang H. Expressions of programmed death (PD)-1 and PD-1 ligand (PD-L1) in cervical intraepithelial neoplasia and cervical squamous cell carcinomas are of prognostic value and associated with human papillomavirus status. J Obstet Gynaecol Res. 2017;43(10):1602-1612. Doi: 10.1111/jog.13411.
[23] Saglam O, Conejo-Garcia J. PD-1/PD-L1 immune checkpoint inhibitors in advanced cervical cancer. Integr Cancer Sci Ther. 2018;5(2):1000272. Doi: 10.15761/icst.1000272.
[24] Shelly D, Sharma P, Mishra P, Mulajker D, Bisht N, Mukundan H, et al. Assessment of programmed death ligand 1 (PD-L1) expression in cervical intraepithelial neoplasia and carcinoma cervix. Med J Armed Forces India. 2024;81(Suppl1):S11-S16. Doi: 10.1016/j.mjafi.2024.02.009.

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