ORIGINAL ARTICLE

Unveiling the role of Programmed Cell Death Ligand-1 (PDL-1) expression in cervical squamous cell carcinoma: Clinical insights and pathological implications

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ABSTRACT

Background: Squamous Cell Carcinoma Cervix (SCC) is a major contributor to cancer-related mortality, closely linked to chronic HPV infection. Programmed Cell Death Ligand-1 (PD-L1) has surfaced as a prospective biomarker in several cancers, including cervical squamous cell carcinoma (SCC); however, its clinical and pathological relevance in untreated patients has not yet been thoroughly investigated.

Methods: This cross-sectional study included 66 untreated patients diagnosed with cervical SCC, with clinicopathological data and formalin-fixed paraffin-embedded tissue samples collected from Universitas Hasanuddin Teaching Hospital. PD-L1 expression was evaluated using the Tumor Proportion Score (TPS) and categorized as negative (<1%), weakly positive (1–9%), and strongly positive (≥10%). Bivariate methods were used to investigate at the associations between PD-L1 expression and tumor characteristics including stage, differentiation, lymphovascular space invasion (LVSI), and tumor size.

Results: Strong PD-L1 expression (≥10%) was significantly more frequent in locally advanced and metastatic stages (p = 0.036). The highest level of PD-L1 expression was observed in tumors which were poorly differentiated; Whereby 84.9% of these tumors exhibited strong expression. No significant correlation was found

Received: 9 November 2025 | Accepted: 18 December 2025

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between PD-L1 expression and LVSI or tumor size. Host factors including age, sexual history, parity, and contraceptive use demonstrated no correlation with PD-L1 expression.

Conclusion: The study showed that PD-L1 expression is associated with advanced stages and poor differentiation in cervical SCC, pointing to its potential role in guiding future treatment decisions. (www.actabiomedica.it)

Key words: squamous cell carcinoma, PD-L1, cervical, HPV, IHC

Introduction

Cervical cancer remains an important cause of morbidity and mortality among women worldwide. It is associated with 650,000 new cases a year and over 340,000 deaths annually (1). Cervical cancer is considered to be one of the serious public health problems in Indonesia, with 17.2% of the total cases and an estimated death toll of 21,003 cases per year (2). The most frequent histology is Squamous cell carcinoma (SCC) which is closely related to persistent infection of high-risk Human Papillomavirus species, in particular HPV 16 and 18 (3). The oncoproteins of the virus E6 and E7 are known to be important in the process that brings an HPV-infected cell to a cancerous one thanks to their function in stimulation of degradation or repression of tumor suppressor genes such as p53 and retinoblastoma (Rb). The inactivation of this gene leads to a blockage of the cell cycle and uncontrolled growth (4). Staging is also important for determining options for treatment in cervical cancer. Molecular markers that can serve as a measure of the course of the disease and response to therapy are urgently required. One of the biomarkers is the PD-L1-Programmed Cell Death Ligand 1, which has grabbed much attention as it allows the immune cells to find it difficult in seeking out cancer cells. PD-L1 is a kind of protein that exists on the outside of cancer cells and attaches to another type of immune cell called T cells by binding to its receptor PD-1, thus hindering the immune function and curbing their attack on tumor (5). Studies have demonstrated that PD-L1 is expressed in various cancers including SCC and proposed PD-L1 as one of the targetable markers for immune checkpoint inhibitors (ICIs) (6). Currently, no studies have yet explored the association between PD-L1 expression and clinical pathology factors including tumor stage, degree of differentiation and lymphovascular space invasion (LVSI) in cervical SCC. The associations between PD-L1 and different clinicopathological features are also unclear, furthermore, previous studies suggested that PD-L1 could be a risk factor of cervical cancer. Well-ordered researches are further required to elucidate the value of PD-L1 as prognostic mark and therapeutic target (6). The aim of the current study was to investigate PD-L1 expression in cervical SCC and its association with tumor stage, grade, LVSI and other clinical factors.

Methods

The studied group consisted of 66 patients with histopathologically diagnosed cervical squamous cell carcinoma. The eligibility criteria included formalin-fixed, paraffin-embedded specimens and no previous cancer treatment. Patients with insufficient medical records, other malignancies, or significant comorbidities were excluded. The data collection process involved demographic and clinical details gathered from structured interviews and medical charts. PD-L1 expression was evaluated by IHC on tumor 3–4 μm sections: Antigen retrieval was performed using Tris-EDTA buffer (pH 9.0) for 10 min in a microwave at 96°C. Immunohistochemical staining was performed using a monoclonal anti–PD-L1 antibody (clone GTX104763, GeneTex). Detection was carried out using a polymer-based detection system with diaminobenzidine (DAB) as chromogen. PD-L1 expression was evaluated using the Tumor Proportion Score (TPS) and categorized as negative (<1%), weakly positive (1–9%), and strongly positive (≥10%). For statistical analysis, negative and weakly positive cases were

grouped as <10%. Data were analyzed utilizing SPSS version 26 (IBM Corp.). Descriptive statistics and Chi-square tests were utilized, with statistical significance established at $p < 0.05$. The Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (No. 123/KEPK/UNHAS/2024) approved this study, which was executed out in compliance with the Declaration of Helsinki. All participants signed informed consent, ensuring voluntary as well as confidential involvement with data anonymized.

Result

A total of 66 patients with cervical squamous cell carcinoma were analyzed. The mean age was 47.1 ± 8.6 years, and most patients were within the 45–54-year range. The majority were multiparous and reported having a single sexual partner. Hormonal contraception was the predominant method of birth control, while only a minority used non-hormonal methods or none at all. Most patients presented with locally advanced disease, and poorly differentiated tumors were the most frequent histologic subtype. Lymphovascular space invasion was detected in nearly 40% of cases, and tumors ≥ 4 cm were predominant. Expression of PD-L1 showed an equal distribution, with 50% exhibiting strong expression (≥10%) and 50% weak expression (<10%). (Figure 1).

Clinicopathological characteristics of SCC with PD-L1 expression are summarized in Figure 2. There was a significant association between PD-L1 expression and both cancer stage ($p = 0.036$) and differentiation grade ($p < 0.001$). Strong PD-L1 expression was more frequent in locally advanced and metastatic stages, as well as in poorly differentiated tumors. No significant correlation was found between PD-L1 expression and LVSI status ($p = 0.450$) or tumor size ($p = 1.000$).

Immunohistochemical analysis of PD-L1 expression was illustrated through membranous staining, categorized into weak and strong expression. Some examples of this staining can be seen in Figure 3. Panels A show negative PD-L1 expression (<1%), panel B shows weak expression (1–9%), while panels C–E demonstrate strong PD-L1 expression (≥10%).

No significant associations were found between host-related factors and PD-L1 expression, as shown

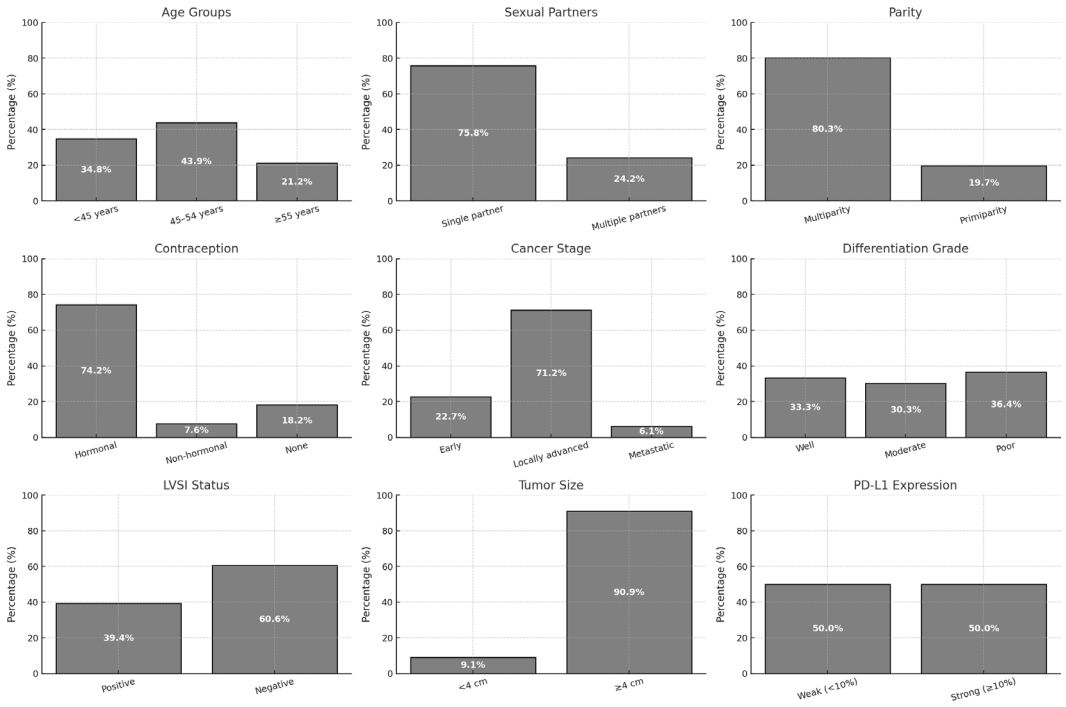

Figure 1. Sample characteristics.

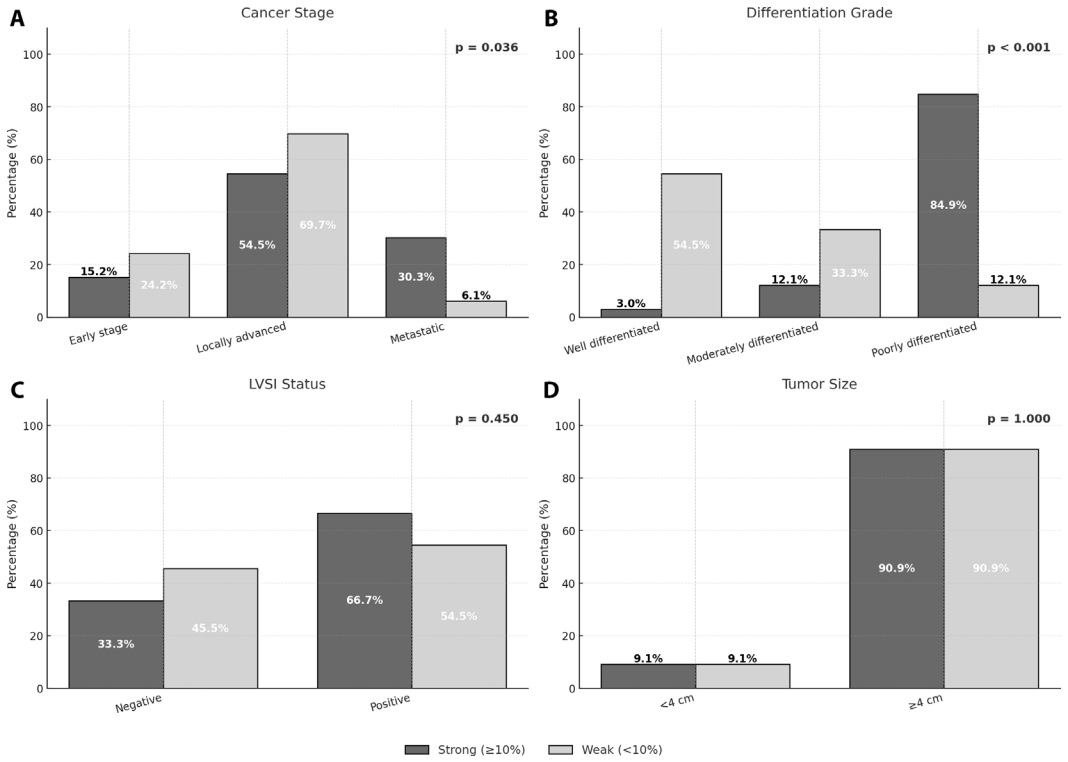

Figure 2. Clinicopathological features of cervical squamous cell carcinoma with PD-L1 expression.

in Figure 4. The distribution of PD-L1 expression was comparable across age groups (p = 0.704) and did not differ according to the number of sexual partners (p = 0.389). Similarly, parity (p = 1.000) and contraceptive use (p = 0.896) showed no meaningful relationship with PD-L1 expression.

Discussion

This study examined SCC of the cervix, the most common form of cervical cancer, representing 70–90% of all global cases. The average age of the participants was 47.14 ± 8.58 years, with the largest group (43.9%) being between 45 and 54 years old. This conclusion is consistent with widespread global trends, indicating that cervical cancer primarily impacts middle-aged women following an extended duration of persistent HPV infection that advances to malignancy (6). This highlights the importance of early screening programs, particularly for women of childbearing age (7). The study showed that most of the patients (75.8%) had only had one sexual partner before. Although most patients reported having a single lifetime sexual partner, this finding should be interpreted in the sociocultural context of Indonesia, where long-term monogamous relationships are common. The risk of cervical cancer remains strongly associated with persistent high-risk HPV infection rather than the absolute number of sexual partners alone; it simply highlights the fact that in places like Indonesia, where most women diagnosed with cervical cancer are married and have a long-term partner, this is the case. It is in keeping with current studies that demonstrate having more than one child increases the risk of cervical cancer because 80.3% of the patients had more than one child. This is mostly because of stress that comes back after giving birth, changes in hormones, and a higher chance of getting HPV again (8). A total of 74.2% of participants reported using hormonal contraception, which represented the most prevalent method for pregnancy prevention. This observation is consistent with previous studies, indicating that prolonged exposure to hormonal contraceptives may elevate the risk of cervical

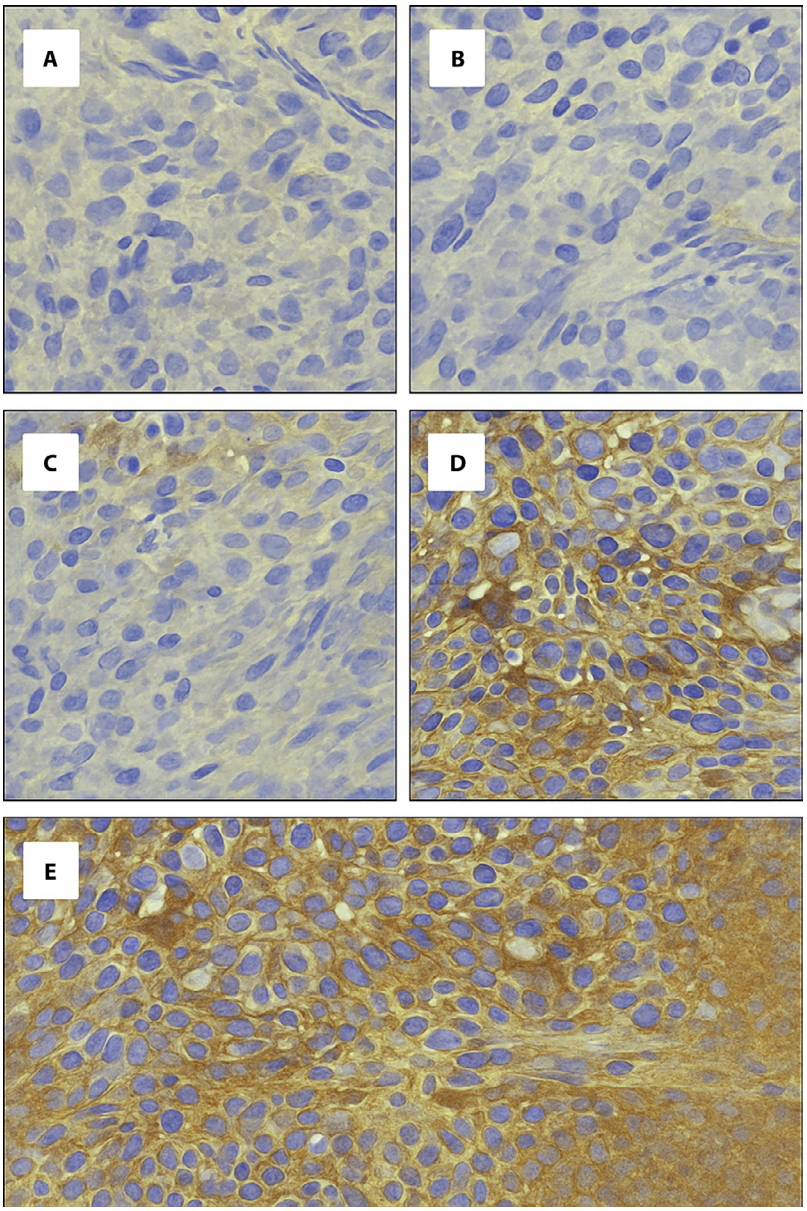

Figure 3. (A) Negative PD-L1 expression (<1%); (B) Weak PD-L1 expression (1–9%); (C–E) Strong PD-L1 expression (≥10%).

cancer, though the magnitude of this effect depends on duration of use and several additional variables (9,10). These findings highlight the need for an integrated preventive approach encompassing HPV vaccination and regular screening, rather than relying solely on contraceptive methods as a preventive measure (11). Analysis of clinical staging revealed that 71.2% of patients presented with locally advanced disease, a pattern that mirrors global trends, particularly in regions where screening programs are not routinely implemented (12). The high proportion of advanced-stage cervical cancer cases in Indonesia underscores the urgent necessity for enhanced national screening and early detection programs, as early diagnosis markedly improves both survival rates and prognosis (13,14).

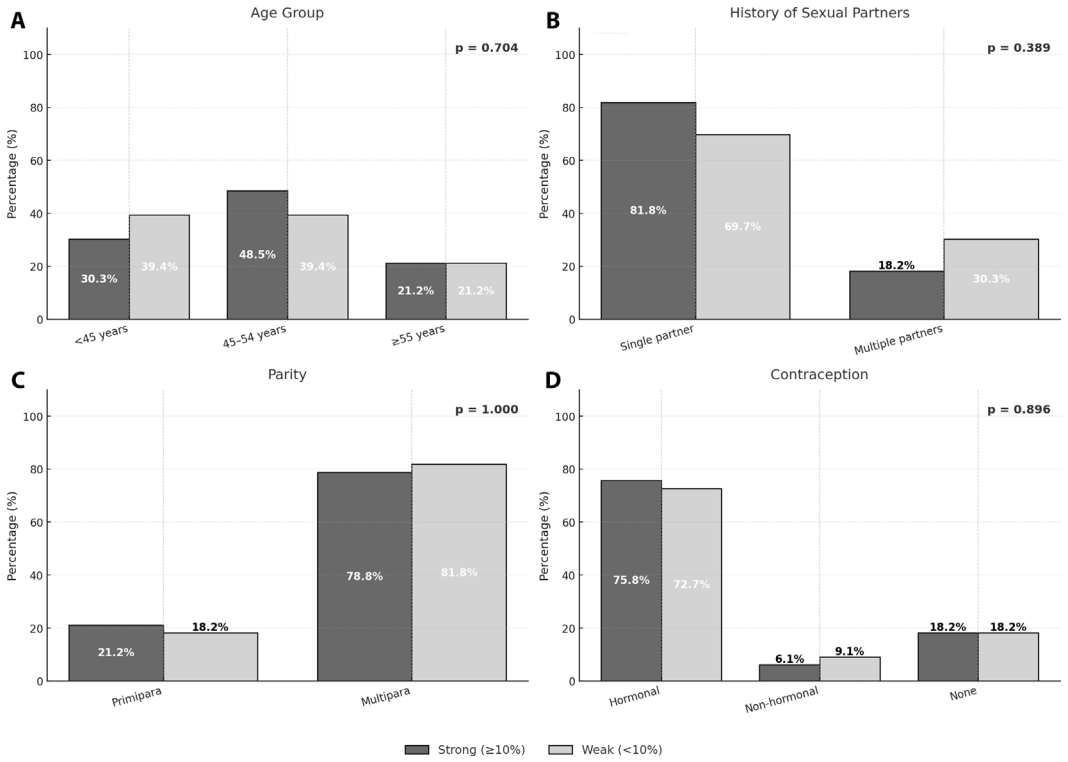

Figure 4. Association between host-related factors and PD-L1 expression in cervical squamous cell carcinoma.

The relationship between PD-L1 expression and clinicopathological factors

This study demonstrated a significant association between tumor stage and PD-L1 expression levels (p = 0.036). PD-L1 expression increased in advanced stages and declined in earlier disease stages. This pattern supports the hypothesis that the PD-1/PD-L1 axis and related immune checkpoint pathways become progressively activated as cervical cancer advances, thereby facilitating immune evasion by tumor cells (12,15). The interaction of PD-L1 on tumor cells with PD-1 receptors on T lymphocytes results in suppression of immune activity, promoting tumor progression—a mechanism commonly referred to as T cell exhaustion (13). PD-L1 expression represents only one component of the tumor immune microenvironment. Interactions between tumor cells, immune infiltrates, and cytokine signaling pathways play a critical role in immune evasion. Assessment using the Combined Positive Score (CPS), which includes immune cell PD-L1 expression, may provide a more comprehensive evaluation and should be considered in future studies. The observation that poorly differentiated tumors exhibited higher PD-L1 expression aligns with prior research demonstrating elevated PD-L1 levels in aggressive and genetically unstable malignancies (6,16). Many poorly differentiated cancers harbor genetic mutations capable of triggering immune responses, consequently upregulating PD-L1 as a mechanism of immune evasion. This association is further substantiated by the role of HPV oncoproteins E6 and E7, which enhance PD-L1 expression through activation of the PI3K/AKT and MAPK signaling pathways mechanisms commonly implicated in aggressive cervical carcinoma phenotypes (16,17). A non-significant association was identified between LVSI status and PD-L1 expression (p = 0.450). Although LVSI serves as a valuable indicator of potential metastatic dissemination, it does not always correlate with PD-L1 expression. This discrepancy likely reflects variations in the immune microenvironment and the tumor's immune-evasive capacity. These findings are consistent with previous reports suggesting that PD-L1 modulation is governed by immune-related rather than purely anatomical parameters.

The levels of PD-L1 expression and tumor size

There was no statistically significant correlation between PD-L1 expression and tumor size ($p = 1.000$). Both small (<4 cm) and large (≥4 cm) tumors displayed similar patterns of PD-L1 expression. This indicates that tumor size may not serve as a dependable predictor of immune checkpoint activity, as PD-L1 expression is probably affected by molecular and immunological regulatory mechanisms within the tumor microenvironment, rather than being exclusively determined by tumor size (6,18).

PD-L1 expression and host factors

No significant associations were detected between PD-L1 expression and host-related characteristics, including age, parity, number of sexual partners, and contraceptive use. While these factors are important for understanding the epidemiology of cervical cancer, they did not exert a measurable effect on PD-L1 expression in this study. The findings suggest that local immune dynamics, such as cytokine milieu, immune cell infiltration, and HPV oncoprotein activity, are more influential in regulating PD-L1 expression (7,19,20).

The future of clinical practice

The data indicate that PD-L1 expression may represent a valuable biomarker for immunotherapeutic interventions, especially in locally advanced and metastatic cervical cancer. The observed relationship between PD-L1 expression and disease stage suggests potential for identifying patients most likely to benefit from immune checkpoint inhibitors, such as pembrolizumab, which have demonstrated efficacy in tumors with high PD-L1 expression (10,11). Nevertheless, PD-L1 expression alone does not consistently predict tumor progression or treatment response, underscoring the necessity for a broader evaluation of the tumor microenvironment when considering immunotherapy eligibility (8,16).

Limitations and future prospects

Although this study provides important insights into PD-L1 expression in cervical squamous cell carcinoma (SCC), certain limitations must be acknowledged. The cross-sectional design restricts causal inference regarding the relationship between PD-L1 expression and disease evolution. Furthermore, being a single-center study, the findings may not fully represent broader populations. Future investigations should employ larger, multicenter cohorts with longitudinal follow-up to validate these results. Additionally, combining PD-L1 assessment with complementary biomarkers, such as HPV DNA status, tumor mutational burden (TMB), and immune cell infiltration, may enable more accurate prognostication and personalized therapeutic strategies. Another limitation of this study is the exclusive use of TPS without CPS evaluation, which may underestimate the contribution of immune cells within the tumor microenvironment (20).

Conclusion

In conclusion, our study shows PD-L1 expression may represent an important biomarker for finding cervical squamous cell carcinoma (SCC) patients who might be able to get immunotherapy, especially when the cancer is locally advanced or has metastated. The relationship between PD-L1 expression and tumor stage may aid physicians in identifying future therapy options; however, additional research is necessary to fully comprehend its influence on treatment efficacy. PD-L1 expression should not be the sole factor considered when selecting treatment options. The results show that when choosing immunotherapy for cervical SCC patients, it's important to take other things into account in the immune microenvironment.

Acknowledgments: The authors would like to express their gratitude to the staff of the Department of Obstetrics and Gynecology and the Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University, for their technical assistance and continuous support throughout the completion of this study.

Ethical Approval: This study was approved by the Ethics Committee of the Faculty of Medicine, Hasanuddin University (No. 123/KEPK/UNHAS/2024) and conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock

ownership, equity interests, patent/licensing arrangements, etc.) that might give rise to a conflict of interest with respect to the submitted article.

Declaration on the Use of AI: No artificial intelligence tools were used in the writing or editing of this manuscript.

Authors Contributions: YS (conceptualized the study, designed the research protocol, and drafted the manuscript). SA (contributed to data collection, clinical supervision, and critical revision of the manuscript). SS (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). RM (conducted immunohistochemical examinations and assisted with pathological data validation). AAZ (performed the statistical analysis, data interpretation, and contributed to manuscript editing). All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

References

1. Sung H, Ferlay J, Siegel RL, et al Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2023;71(3):209-249. doi:10.3322/caac.21660
2. International Agency for Research on Cancer Global Cancer Observatory. Cervical cancer incidence and mortality statistics in Indonesia. 2020. Available from: https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf
3. World Health Organization Human papillomavirus (HPV) and cervical cancer. WHO Fact Sheet. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/cervical-cancer
4. Arbyn M, Weiderpass E, Bruni L, et al Estimates of incidence and mortality of cervical cancer in 2018: A worldwide analysis. Lancet. 2020;385(9961):1001-1011. doi:10.1016/S0140-6736(15)60636-0
5. Garcia C, Ring KL, Lemech C, et al Programmed cell death ligand-1 (PD-L1) and its role in immune evasion in cancer. Nat Rev Immunol. 2018;18(7):439-449. doi:10.1038/s41577-018-0005-4
6. Heeren AM, Punt S, Bleeker MC, et al Prognostic effect of PD-L1 expression in cervical cancer. Cancer Immunol Res. 2016;4(3):225-234. doi:10.1158/2326-6066.CIR-15-0174
7. Liu X, Liu B, Li J, et al HPV E6 and E7 oncoproteins in cervical cancer progression. J Clin Oncol. 2017;35(1):28-34.
8. Singh R Multiparity and cervical cancer risk: A review of epidemiological studies. Asian Pac J Cancer Prev. 2023;24(7):1905-1912. doi:10.31557/APJCP.2023.24.7.1905
9. Koliopoulos G, Nyaga VN, Santesso N, et al Cytology versus HPV testing for cervical cancer screening in the general population. Int J Cancer. 2018;143(5):1030-1040. doi:10.1002/ijc.31373
10. Huang J, Olawaiye AB, Clark LH, et al Pembrolizumab in cervical cancer: Results from KEYNOTE-158. Lancet Oncol. 2022;23(5):639-649. doi:10.1016/S1470-2045(22)00070-0
11. Marabelle A, Fakih M, Lopez J, et al Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: Results from the KEYNOTE-158 study. J Clin Oncol. 2020;38(28):3284-3292. doi:10.1200/JCO.19.02105
12. Choi YJ, Park JS HPV and cervical cancer: Epidemiology and prevention. Int J Gynaecol Obstet. 2016;134(2):216-220. doi:10.1016/j.ijgo.2015.11.021
13. Ghosh A, Kumar S, Kumar A Immune evasion in cancer and implications for immunotherapy. JAMA Oncol. 2021;7(8):1145-1152. doi:10.1001/jamaoncol.2021.1234
14. Campos-Parra AD, Maffuz-Aziz A, Arrieta O The role of the tumor microenvironment in cervical cancer: Implications for immunotherapy. Cerv Cancer J. 2022;10(2):220-230.
15. Lantuejoul S, Sound-Tsao M, Cooper WA, et al PD-L1 testing for lung cancer in 2019: Perspective from the IASLC pathology committee. Eur Respir J. 2020;55(2):1901403. doi:10.1183/13993003.01403-2019
16. Brito MJ, Carvalho A, Medeiros R Immune microenvironment and PD-L1 expression in cervical cancer. J Cancer Immunol. 2023;22(4):340-352.
17. Feng Z, Wen H, Ju X Tumor-infiltrating lymphocytes and PD-L1 expression in cervical cancer. Int J Gynecol Cancer. 2018;28(8):1554-1563. doi:10.1097/IGC.0000000000001354
18. Rotman Y, Brown M, Rosenthal A Immune microenvironment and PD-L1 in cervical cancer. J Cancer Res Clin Oncol. 2020;146(9):2403-2411. doi:10.1007/s00432-020-03292-2
19. Wu L, Saxena S, Awaji M Checkpoint inhibitors and tumor immunity: Mechanisms and clinical implications. Front Immunol. 2019;10:1225. doi:10.3389/fimmu.2019.01225
20. Reddy S, Zhuang Y, Kaur P The role of PD-L1 in cervical cancer: An emerging immunotherapy target. J Immunother. 2017;39(6):129-139.