

Programmed Death-Ligand 1 Immunohistochemical Expression in Invasive Urothelial Carcinoma of the Bladder: Association with Lymphovascular Invasion

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Abstract

Introduction: Invasive urothelial carcinoma of the urinary bladder is a heterogeneous malignancy with variable biological behavior and clinical outcomes. Programmed death-ligand 1 (*PD-L1*) immunohistochemical expression has been widely investigated as a potential biomarker in urothelial carcinoma; however, its clinicopathological significance remains inconsistent. **Materials and Methods:** This analytical cross-sectional study evaluated the clinicopathological characteristics of invasive urothelial carcinoma of the bladder and analyzed their association with *PD-L1* immunohistochemical expression. A total of 32 formalin-fixed, paraffin-embedded tissue samples diagnosed over a three-year period were included. The variables assessed comprised age, sex, lympho-vascular invasion, perineural invasion, tumor-infiltrating lymphocytes, and histological subtypes based on the WHO Classification of Urinary and Male Genital Tumours, 5th edition (2022). *PD-L1* immunohistochemistry was performed using a monoclonal rabbit anti-human *PD-L1* antibody (GeneAb™; 1:100 dilution), with tonsil tissue used as a positive control. *PD-L1* expression was evaluated using the Combined Positive Score (CPS), and a CPS of ≥ 10 was considered positive. **Results:** *PD-L1* expression was identified in 3 of 32 cases (9.4%). A statistically significant association was found between *PD-L1* expression and lympho-vascular invasion ($p = 0.033$). No significant association was observed between *PD-L1* expression and tumor-infiltrating lymphocytes or other clinicopathological parameters. **Conclusion:** *PD-L1*-positive cases in this study were identified only in tumors with lympho-vascular invasion. However, because of incomplete clinical staging data and the limited sample size, the clinical significance of this observation remains uncertain and requires further validation in larger studies.

Keywords: Invasive urothelial carcinoma, *PD-L1*, immunohistochemistry, lympho-vascular invasion, bladder cancer

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Introduction

Bladder cancer most commonly arises from the urothelial lining of the urinary bladder, with urothelial carcinoma representing the predominant histological subtype. Globally, bladder cancer ranks among the most common malignancies and remains an important cause of cancer-related mortality. In 2022, approximately 614,298 new cases of bladder cancer and 212,536 related deaths were reported worldwide [1, 2]. Bladder cancer occurs more frequently in men, with a reported male-to-female ratio of approximately 5:1, and its incidence increases with advancing age [1].

The therapeutic approach to urothelial carcinoma is primarily determined by the depth of tumour invasion [3]. Neoadjuvant or adjuvant treatment strategies are selected according to tumour stage and the presence or absence of metastatic disease [4]. In recent years, immunotherapy targeting the programmed cell death-1 (*PD-1*) pathway and its ligand, programmed death-ligand 1 (*PD-L1*), has emerged as an important treatment option, particularly in patients who are refractory to or ineligible for platinum-based chemotherapy [5, 6]. *PD-L1* expression can be assessed by immunohistochemistry and has

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become one of the most extensively studied biomarkers in immune checkpoint inhibitor therapy. Several studies have demonstrated associations between *PD-L1* expression and therapeutic response; however, the clinicopathological relevance of *PD-L1* expression in urothelial carcinoma remains controversial [5, 6]. Variability in study design, antibody clones, scoring systems, and tumour heterogeneity may contribute to inconsistent findings regarding the relationship between *PD-L1* expression and histopathological characteristics.

Previous studies have suggested that *PD-L1* expression may be associated with aggressive tumour features, including high grade, advanced stage, lympho-vascular invasion, and specific histological variants. Nevertheless, data concerning the relationship between *PD-L1* immunohistochemical expression and lympho-vascular invasion, tumour-infiltrating lymphocytes, and histological subtypes in invasive urothelial carcinoma remain limited and inconclusive, particularly in routine diagnostic practice.

Data regarding *PD-L1* immunohistochemical expression in invasive urothelial carcinoma from Indonesian populations remain limited, particularly studies applying the WHO Classification of Urinary and Male Genital Tumours, 5th edition (2022), with Combined Positive Score (CPS)-based evaluation in routine diagnostic practice. In addition, variability in antibody clones and scoring systems continues to contribute to inconsistent findings across studies.

Therefore, this study aimed to evaluate the clinicopathological characteristics of invasive urothelial carcinoma of the bladder and to analyze their association with *PD-L1* immunohistochemical expression, with particular emphasis on lympho-vascular invasion, tumour-infiltrating lymphocytes, and histological subtypes as defined by the WHO Classification of Urinary and Male Genital Tumours, 5th edition (2022).

Materials and Methods

Study Design

This was an analytical study with a cross-sectional design.

Study Population and Samples

The study population comprised patients who underwent biopsy or transurethral resection of bladder tumour and were histopathology diagnosed with invasive urothelial carcinoma based on haematoxylin-eosin staining. A total of 32 formalin-fixed, paraffin-embedded tissue samples collected over a three-year period were included according to predefined inclusion and exclusion criteria. Consecutive sampling was applied.

Histopathological Evaluation

The clinicopathological variables evaluated in this study included age, sex, clinical stage, lympho-vascular invasion (LVI), perineural invasion (PNI), tumour-infiltrating lymphocytes (TILs), and histological subtypes. Histological classification and subtype determination were

performed in accordance with the WHO Classification of Urinary and Male Genital Tumours, 5th edition (2022) [7].

Immunohistochemistry for *PD-L1*

Immunohistochemical staining for *PD-L1* was performed using a monoclonal rabbit anti-human *PD-L1* antibody (GeneAb™) at a dilution of 1:100 (GenomeMe). Tonsil tissue was used as a positive control. *PD-L1* expression was evaluated based on membranous and/or cytoplasmic staining in tumour cells, lymphocytes, and macrophages.

PD-L1 Scoring System

PD-L1 immunohistochemical expression was assessed using the Combined Positive Score (CPS), calculated as follows [8]:

$$\text{CPS} = (\text{number of } PD-L1\text{-positive tumour cells, lymphocytes, and macrophages} / \text{total number of viable tumour cells}) \times 100$$

A CPS value of ≥ 10 was considered positive.

Data Collection

Samples were identified through the pathology data storage system. Slide and paraffin block identification numbers corresponding to histopathological diagnoses of invasive urothelial carcinoma were retrieved and reviewed to confirm eligibility.

Statistical Analysis

Descriptive statistics were used to summarize the frequency distribution of clinicopathological characteristics. Associations between *PD-L1* immunohistochemical expression and clinicopathological variables were analysis using Fisher's exact test or the Chi-square test, as appropriate. A p-value of < 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia (Approval No. 1088/KEPK/USU/2024). As the study used archived histopathological specimens and secondary data, informed consent from individual patients was waived by the ethics committee.

Results

The clinicopathological characteristics of invasive urothelial carcinoma are summarized in Table 1. The correlations between lympho-vascular invasion and *PD-L1* immunohistochemical expression and between tumour-infiltrating lymphocytes and *PD-L1* immunohistochemical expression are presented in Tables 2 and 3, respectively. Representative *PD-L1* immunohistochemical staining patterns are shown in Figure 1.

As shown in Table 1, invasive urothelial carcinoma was predominantly observed in male patients, accounting

Table 1. Clinicopathological Characteristics of Invasive Urothelial Carcinoma Cases

Variable	Frequency (n=32)	Percent (%)
Sex		
Male	26	81.3
Female	6	18.7
Age		
<30 years	0	0
30-39 years	2	6.2
40-49 years	2	6.2
50-59 years	12	37.6
≥ 60 years	16	50
Clinical stage		
Stage 1	-	-
Stage 2	-	-
Stage 3	1	3.1
Stage 4	-	-
Not Available	31	96.9
Lympho-vascular invasion (LVI)		
Absent	21	65.6
Present	11	34.3
Perineural invasion (PNI)		
Absent	32	100
Present	0	0
Tumor-infiltrating lymphocytes (TILs)		
Mild	16	50
Moderate	6	18.7
Severe	10	31.3
Histological subtype		
Conventional urothelial carcinoma	0	0
Urothelial carcinoma with squamous differentiation	12	37.6
Urothelial carcinoma with glandular differentiation	0	0
Urothelial carcinoma with trophoblastic differentiation	0	0
Nested urothelial carcinoma	2	6.2
Large nested urothelial carcinoma	0	0
Tubular and microcystic urothelial carcinoma	0	0
Micropapillary urothelial carcinoma	2	6.2
Lymphoepithelioma-like urothelial carcinoma	0	0
Plasmacytoid urothelial carcinoma	0	0
Giant cell urothelial carcinoma	0	0
Lipid-rich urothelial carcinoma	5	15.7
Clear cell urothelial carcinoma	11	34.3
Sarcomatoid urothelial carcinoma	0	0
Poorly differentiated urothelial carcinoma	0	0
PD-L1 immunohistochemical expression		
Negative	29	90.6
Positive	3	9.4

Table 2. Correlation between Lymphovascular Invasion (LVI) and *PD-L1* Immunohistochemical Expression

<i>PD-L1</i> immunohistochemical expression					p-value*
LVI	Positive		Negative		
	n	%	n	%	
Absent	0	0	21	100	0.033
Present	3	27.3	8	72.7	
Total	3		29		

*Fisher's Exact test

for 26 cases (81.3%), whereas female patients comprised 6 cases (18.7%). Most patients were aged 60 years or older (16 cases, 50.0%), followed by those aged 50-59 years (12 cases, 37.5%). No cases were identified in patients younger than 30 years.

Clinical stage information was unavailable for most cases (31/32, 96.9%), with only one case documented as stage III. Lympho-vascular invasion was identified in 11 cases (34.4%), whereas 21 cases (65.6%) showed no evidence of lympho-vascular invasion. Perineural invasion was not observed in any of the examined samples. Therefore, stage-based correlation analysis could not be performed. Regarding the tumour immune microenvironment, tumour-infiltrating lymphocytes were most frequently classified as mild in 16 cases (50.0%), followed by severe TIL infiltration in 10 cases (31.3%) and moderate infiltration in 6 cases (18.7%).

Histologically, the most common subtype was urothelial carcinoma with squamous differentiation, identified in 12 cases (37.5%), followed by clear cell urothelial carcinoma in 11 cases (34.4%). Other histological variants, including nested urothelial carcinoma and micropapillary urothelial carcinoma, were infrequent, each observed in 2 cases (6.3%). Lipid-rich urothelial carcinoma accounted for 5 cases (15.6%). *PD-L1* immunohistochemical expression was negative in most cases (29/32, 90.6%), whereas positive expression was observed in 3 cases (9.4%).

As shown in Table 2, *PD-L1* immunohistochemical expression was observed only in cases with lympho-vascular invasion. Among tumours with lympho-vascular invasion, *PD-L1* positivity was found in 3 cases (27.3%), while 8 cases (72.7%) were *PD-L1* negative. In contrast, none of the tumours without lympho-vascular invasion

Table 3. Correlation between Tumor- Infiltrating Lymphocytes (TILs) and *PD-L1* Immunohistochemical Expression

	<i>PD-L1</i> immunohistochemical expression				p-value*
TILs	Positive		Negative		
	n	%	n	%	
Mild	2	12.5	14	87.5	0.565
Moderate	1	16.7	5	83.3	
Severe	0	0	10	100	
Total	3		29		

*Chi Square test

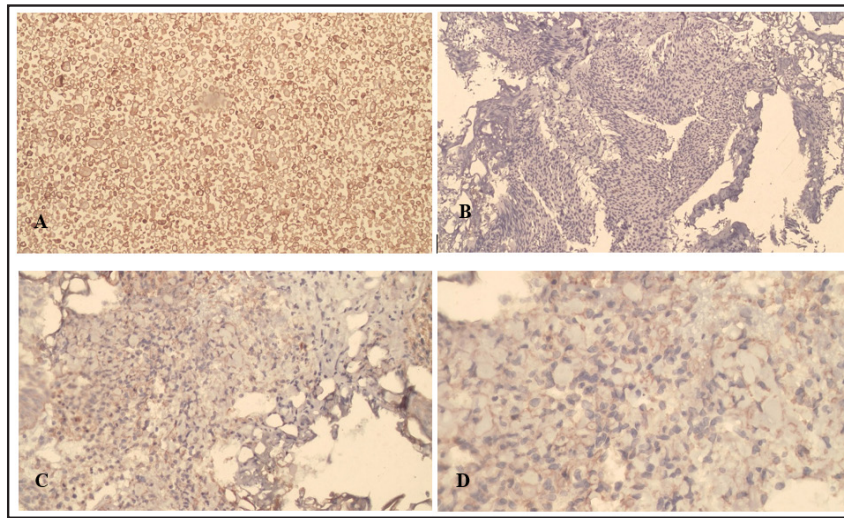


Figure 1. *PD-L1* immunohistochemical staining. (A) Tonsil tissue as positive control. (B) Negative *PD-L1* immunohistochemical expression ($\times 100$). (C) Positive *PD-L1* immunohistochemical expression ($\times 100$). (D) Positive *PD-L1* immunohistochemical expression showing membranous staining ($\times 400$).

showed *PD-L1* expression; all 21 cases (100%) were *PD-L1* negative. Fisher's exact test demonstrated a statistically significant association between lympho-vascular invasion and *PD-L1* immunohistochemical expression ($p = 0.033$).

As presented in Table 3, *PD-L1* immunohistochemical expression was detected in tumours with mild and moderate TILs. Among cases with mild TILs, *PD-L1* positivity was observed in 2 cases (12.5%), while 14 cases (87.5%) were *PD-L1* negative. In the moderate TIL group, *PD-L1* positivity was found in 1 case (16.7%), whereas 5 cases (83.3%) were negative. No *PD-L1* immunohistochemical expression was observed in tumours with severe TILs, as all 10 cases (100%) were *PD-L1* negative. Statistical analysis showed no significant association between tumour-infiltrating lymphocytes and *PD-L1* immunohistochemical expression ($p = 0.565$).

Discussion

In the present study, invasive urothelial carcinoma was predominantly observed in male patients (81.3%), with a male-to-female ratio of 4.3:1. This finding is consistent with previous studies reporting a higher prevalence of urothelial carcinoma among men [6,9-11]. The higher incidence in male patients has been attributed to several factors, including smoking habits, occupational exposure, hormonal influences, and genetic susceptibility. Testosterone and androgen receptor-mediated signal have also been proposed to contribute to urothelial carcinogenesis [12].

In this study, invasive urothelial carcinoma was most frequently identified in patients aged 60 years or older, with a mean age of 58.97 years and a median age of 59.5 years. This finding is in line with previous reports indicating that urothelial carcinoma predominantly affects older individuals [10, 11, 13]. Urothelial carcinoma in younger patients is relatively uncommon and may be associated with specific risk factors, including genetic

predisposition and chronic inflammatory conditions [14].

Lympho-vascular invasion was identified in 34.3% of cases, and *PD-L1* positivity was observed exclusively in tumour with lympho-vascular invasion, with a statistically significant association ($p = 0.033$). Lympho-vascular invasion is a well-recognized marker of tumour aggressiveness because it reflects the capacity of tumour cells to invade vascular and lymphatic channels and potentially disseminate to distant sites. Previous studies have likewise emphasized the prognostic relevance of lympho-vascular invasion in urothelial carcinoma [15-16]. Some studies have demonstrated a significant association between *PD-L1* expression and vascular or lymphatic invasion [16], whereas others did not find a significant relationship [17]. These discrepancies may be related to differences in antibody clones, scoring systems, sample size, and tumour heterogeneity. The present study provides additional regional data from North Sumatra, Indonesia, using CPS ≥ 10 assessment with the GeneAb™ antibody in routine pathology practice. Although the overall *PD-L1* positivity rate was low, all *PD-L1*-positive cases were identified in tumours with lympho-vascular invasion, supporting a possible association between *PD-L1* expression and lympho-vascular invasion in this study.

Tumour-infiltrating lymphocytes were most commonly classified as mild in the present study, and no significant association was identified between TILs and *PD-L1* immunohistochemical expression ($p = 0.565$). This finding is consistent with the report by Rinonce et al. [18], although other investigators have found a stronger relationship between immune infiltration and *PD-L1* expression [19-21, 23]. The interaction between *PD-L1* expression and TIL density is complex. *PD-L1* expression may be induced not only by immune-mediated mechanisms but also by intrinsic tumour signal pathways such as PI3K-AKT and JAK-STAT activation [20-23]. In addition, TILs may become functionally exhausted, limiting cytokine production and weakening immune-driven *PD-L1* upregulation.

The histological subtype distribution in the present study differed from that reported in most bladder cancer series, with a relatively high proportion of tumour showing variant histological features and absence of conventional urothelial carcinoma. This may partly reflect referral and consultation bias in a tertiary pathology setting, where diagnostically challenging or unusual cases are more frequently encountered.

In addition, certain morphological features, including clear cytoplasmic or lipidized appearance, may overlap with conventional urothelial carcinoma showing divergent differentiation, potentially contributing to interobserver variability in subtype classification. Therefore, the representativeness and generalizability of the present findings should be interpreted cautiously.

In the present study, the most common histopathological subtype was urothelial carcinoma with squamous differentiation, and *PD-L1* positivity was observed only in this subtype. However, the association between histological subtype and *PD-L1* expression did not reach statistical significance. Histopathological subtyping has therapeutic and prognostic implications in bladder cancer, especially because certain variants are associated with more aggressive clinical behavior and distinct treatment considerations [24-26].

PD-L1 immunohistochemical expression is known to vary according to antibody clone, staining platform, scoring system, cutoff value, and interpretation criteria [20,27]. In the present study, *PD-L1* positivity was detected in only 9.4% of cases using the GeneAb™ monoclonal rabbit anti-human *PD-L1* antibody and a CPS cutoff of ≥ 10 . This rate was lower than that reported in several published series of urothelial carcinoma using CPS-based assessment. However, direct comparison is limited because published studies using the identical GeneAb™ antibody clone with the same CPS ≥ 10 threshold in invasive urothelial carcinoma are scarce. Therefore, the lower positivity rate observed in this study should be interpreted cautiously.

Several explanations may account for this finding. First, the low rate may reflect biological differences related to the regional population and histological composition of the cases. Second, technical and pre-analytical factors, including fixation duration, antigen preservation in archived FFPE tissue, antigen retrieval conditions, and staining platform differences, may influence *PD-L1* immunoreactivity. Although the Dako 22C3 pharmDx assay with the Autostainer Link 48 platform is commonly recommended for standardized *PD-L1* assessment, this platform was not available in our institution. Therefore, *PD-L1* immunohistochemistry was performed using the GeneAb™ antibody clone with an alternative laboratory staining protocol. Positive staining in tonsil tissue used as an external control confirmed adequate immunoreactivity. However, differences in antibody clone, staining platform, and assay standardization may have contributed to variability in *PD-L1* positivity rates compared with studies using standardized companion diagnostic assays. Third, CPS interpretation may be affected by tumour heterogeneity and observer-related

variation, particularly when positive immune cells are sparse or unevenly distributed. Therefore, the low *PD-L1* positivity rate in this study should not be interpreted as a definitive biological characteristic, but rather as a finding that requires validation in larger studies using standardized antibody clones, staining protocols, and scoring methods.

This study has several limitations. First, complete clinical stage data were unavailable in most cases, precluding stage-adjusted analysis and raising the possibility of stage-related confounding effects. Second, the relatively small sample size and low number of *PD-L1*-positive cases limited the statistical robustness and generalizability of the findings. Third, the unusual histological subtype distribution may not reflect the broader spectrum of bladder urothelial carcinoma encountered in routine clinical practice. In addition, direct comparison with studies using the identical GeneAb™ antibody clone and CPS ≥ 10 cutoff remains limited. Therefore, the present findings should be interpreted cautiously and considered exploratory in nature. Larger multicenter studies with standardized methodology and comprehensive clinicopathological data are required to validate these observations.

In the present study, *PD-L1*-positive cases were identified only in tumours with lympho-vascular invasion. However, because outcome and survival data were unavailable, the biological and prognostic significance of this finding remains uncertain. Therefore, the observed association should be interpreted as exploratory rather than evidence of clinical utility or prognostic relevance.

In conclusion, in this study, *PD-L1*-positive cases were identified only in tumours with lympho-vascular invasion. However, because of incomplete clinical staging data, unusual histological subtype distribution, and the limited sample size, the observed association should be interpreted cautiously. No significant association was identified between *PD-L1* expression and tumour-infiltrating lymphocytes. Further studies with larger sample sizes and comprehensive clinicopathological and outcome data are required to validate these findings.

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Conflict of Interest

Author declares no conflict of interest

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