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RESEARCH

Association of programmed death ligand 1 expression with urothelial carcinoma grade- A retrospective study in Basrah city

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Abstract

Urothelial carcinoma (UC) is the commonest type of malignancy in the urinary system. The programmed death-ligand 1 (PD-L1) expression plays a key role in tumor immune evasion and could impact prognosis and treatment response, mainly to immune checkpoint inhibitors. This study was designed to assess PD-L1 expression using the Combined Positive Score (CPS) in UC cases from Basrah city and analyze its association with tumor grade, invasiveness, histological type, gender, and age. Fifty cases of UC were involved in this retrospective study. PD-L1 expression was evaluated using immunohistochemistry and quantified by CPS. The tumors were classified by histological grade (low or high), type (squamous or papillary), and invasiveness (invasive or noninvasive). Statistical analysis was performed with SPSS software. PD-L1 expression (CPS > 0) was found in 30% of cases, and it was strongly associated with tumor grade and invasiveness ($p < 0.001$), with higher-grade tumors and muscle-invasive tumors showing elevated levels of expression. These findings confirmed a significant association between PD-L1 expression in relation to tumor grade in UC, indicating its potential role as a prognostic marker and therapeutic target in high-grade tumors. Further studies on larger cohorts and clinical follow-up are recommended.

Keywords PD-L1 · Immunohistochemistry analysis · Urothelial carcinoma · Combined Positive Score

Introduction

Urothelial bladder cancer is the most common and the most frequently diagnosed type of cancer affecting the urinary system in Western countries, ranking seventh worldwide in men and seventeenth in women (Agrawal et al. 2023). Urothelial carcinoma (UC) represents 90% of all bladder cancer cases. Typical diagnosis of UC is typically achieved through a combination of cystoscopic examination, urinary biomarker analysis, and urinary cytology, followed by transurethral resection of the bladder tumor (TURBT) for histopathological evaluation (Germanà et al. 2024). About 50% of patients survive for five years following radical cystectomy (RC). To enhance treatment outcomes, cisplatin-based neoadjuvant chemotherapy (NAC) and adjuvant platinum-based chemotherapy are used (Krafft et al. 2021). However, in the latest few decades, there was non significant improvement in the overall survival rate for patients with metastatic bladder cancer. Recently, advances in immunotherapy, particularly with Immune checkpoint inhibitors (ICIs), have shown significant anti-tumor effects (Li et al. 2020).

Immune checkpoint inhibitors target and block specific proteins that inhibit immune responses, such as programmed death-1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). These proteins suppress the activity of anti-tumor T-cells and are a key mechanism for immune evasion in various solid tumors, including UC, non-small cell lung cancer (NSCLC), and malignant melanoma (Hess et al. 2025; Eckstein et al. 2019). The three stages of the cancer immune-editing process—elimination, equilibrium, and escape—are connected to PD-L1 expression on tumor cells. In the elimination phase, immune cells identify and destroy cancer cells before they become clinically visible. Tumor cells that survive this initial immune attack enter the equilibrium phase, where adaptive immunity influences their immunogenicity and prevents their proliferation (Al Nabhani et al. 2022). In rare cases, mutant tumor cells that evade the immune system can progress to the third phase (escape) by changing surface antigens and producing cytokines and immunosuppressive chemicals, which continue to block immune responses, leading to clinically detectable cancer (Mittal et al. 2014).

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PD-L1 is a cell surface glycoprotein belonging to the B7/CD28 co-stimulatory factor family. It suppresses the immune response by binding to either a potential non-PD-1 receptor or to the programmed cell death receptor 1 (PD-1) on T cells, thereby promoting T cell apoptosis. Furthermore, upregulation of PD-L1 may enable cancer cells to evade immune surveillance, similar to self-antigen recognition, leading to severe impairment of the antitumor immune response. The PD-1/PD-L1 signaling axis may inhibit or deplete activated T cell signaling. (Ding et al. 2019). A high rate of PD-L1 expression on tumor cells is correlated with higher stage and grade and worse prognosis; however, its impact on prognosis remains controversial in cases of UC (Bellmunt et al. 2015). The expression of PD-L1 in UC has yielded inconsistent results across various clinical trials regarding its predictive and prognostic significance. However, several studies have reported an association between PD-L1 overexpression in tumor cells and lymph node metastasis, higher clinical stage, increased recurrence rates, shorter loco-regional failure, and decreased disease-free survival (Kim et al. 2020; Mustafa et al. 2024).

Immunohistochemistry (IHC) assays are the preferred method for evaluating PD-L1 expression in UC. IHC varies in many aspects, including the targeted cell populations, the detection antibodies, and the scoring cutoff values. In addition to the PD-L1 results, the results may be affected by factors such as specimen size, biopsy location, prior treatments like radiation, chemotherapy, or intravesical BCG therapy, and the timing of tissue sampling. Therefore, IHC testing for PD-L1 is fundamental for identifying patients more likely to benefit from immunotherapy and to avoid unnecessary side effects in those less likely to respond (Kim et al. 2020).

This study aims to examine the relationship between PD-L1 expression in urothelial cancer cells and various pathological and clinical features in patients from Basrah, including age, gender, tumor grade, histological type, and muscle invasion.

Methods

This cross-sectional retrospective study analyzed 50 FFPE (formalin-fixed paraffin-embedded) tumor tissues, obtained from transurethral resection of UC and cystectomy specimens. PD-L1 expression was evaluated in the tumor cells, and the combined positive score was calculated.

Case selection

Fifty Cases of UC consist of 45 transurethral specimens and 5 cystectomy specimens. were gathered from the Basrah central lab and the private laboratory in the period between 2020 and 2025. The included specimens were for high-grade disease and low-grade disease with histologic types of UC. The tumors were microscopically classified and graded depending on the 2016 World Health Organization classification system. Pathological staging (pT) was determined based on the TNM classification and included pTa ($n=5$), pT1 ($n=40$), and pT2 ($n=5$).

Tissue PD-L1 using IHC analysis

For the PD-L1 IHC analysis, 50 tumor tissue samples were utilized. The procedure involved 3µm-thick FFPE (formalin-fixed paraffin-embedded) tissue sections using the 22C3 clone (M3653, Agilent/DAKO, Carpinteria, CA, USA). CPS (combined positive score) was used to determine the expression of PD-L1.

The PD-L1 staining was quantified by counting the number of stained cells (tumor and immune cells) and then dividing by the total number of viable tumor cells. The result was multiplied by 100, with a maximum value capped at 100.

Statistics analysis

Statistical analysis was performed using IBM SPSS software (Version 27.0, Armonk, NY, USA: IBM Corp).

T-test, Mann–Whitney U, ANOVA, and Kruskal–Wallis tests were applied at $P \leq 0.05$.

Results

In this study, 50 samples were analyzed, with 80.4% males and 19.6% females, all patients had a confirmed diagnosis of UC (Fig. 1 a). As shown in Fig. 1b, 17 cases (34%) were identified as positive PD-L1, while the other 33 cases (66%) were negative PD-L1 using a cut-off value of 10%. The combined positive score (CPS) is a method used to measure PD-L1 expression in each sample. This score is measured by dividing the count of PD-L1-stained cells (including tumor cells, macrophages, and lymphocytes) by the total number of viable tumor cells, and then multiplying the quotient by 100. CPS acts as an essential biomarker for measuring the response to PD-1/PD-L1 inhibitors in cancer immunotherapy. To determine if there were statistically significant differences in PD-L1 expression between male and female patients, both the t-test and the non-parametric Mann–Whitney U test were conducted. The t-test showed a t-statistic of $t(48)=1.851$ with a p-value of 0.076 (Table 1), suggesting that the difference in CPS between genders didn't match the standard significance level of 0.05. In addition, the Mann–Whitney U test yielded a U value of 227.5 with a p-value of 0.504 (Table 1), confirming the conclusion that there was no statistically significant difference in CPS distribution between male and female patients. These findings

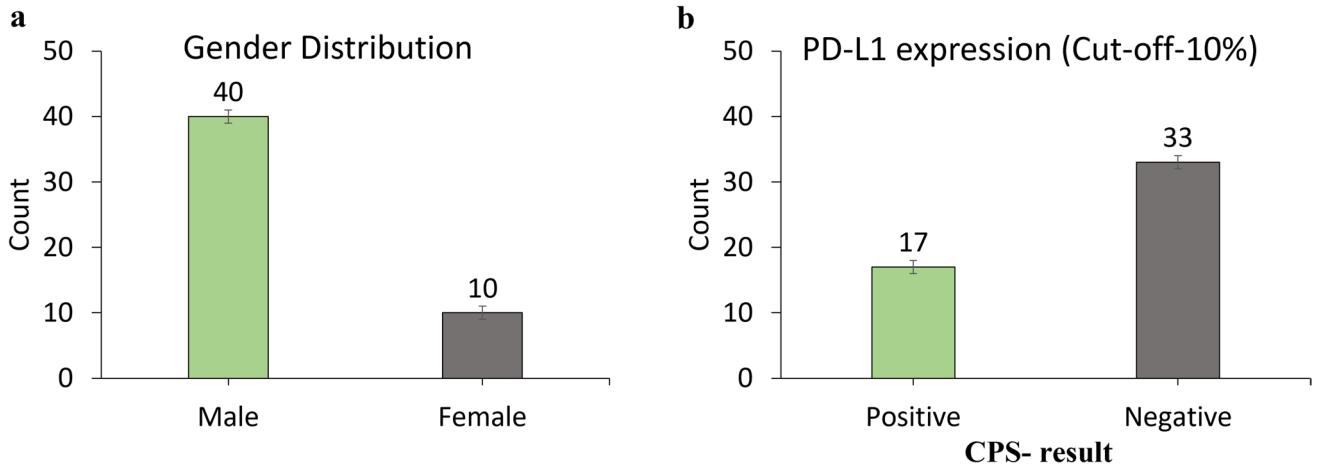

Fig. 1 **a** Gender distribution; **b** PD-L1 expression (Cut-off-10%)

Table 1 T-test and Mann–Whitney U tests to compare the gender association with CPS

Test	Statistical analysis	*p*-value
T-test	1.851	0.076
Mann–Whitney U test	227.5	0.504

Table 2 CPS scores are associated with tumor grade

Grade category	Count	Mean CPS	Std Dev	Min	Max
High Grade	22	0.89	1.16	0	3
low Grade	24	17.5	18.35	0	50
High Grade + Squamous Differentiation	4	80.0	0.0	80	80

confirmed that gender didn't have a significant effect on PD-L1 expression in patients with UC, which may be due to male and female patients might have similar responses to immunotherapies targeting PD-L1 (Liu et al. 2020).

The CPS scores concerning tumor grade exhibited significant differences among various histological subtypes. As shown in Table 2, low-grade ($n=24$) tumors had a significantly higher average CPS of 17.5 ($\pm$18.35), with scores ranging from 0 to 50. In contrast, high-grade tumors ($n=22$) showed a lower average CPS of 0.89 ($\pm$1.16), with a maximum score of 3. Interestingly, the highest PD-L1 expression was found in high-grade tumors with squamous differentiation ($n=4$), and a consistent CPS score of 80. These findings suggest that PD-L1 overexpression may be more closely associated with squamous differentiation rather than solely with increased tumor grade. Table 3 showed that the level of PD-L1 expression varied significantly with tumor

Table 3 CPS scores associated with tumor invasiveness

Invasiveness	Count	Mean CPS	Std Dev	Min	Max
Invasive	44	20.07	27.07	0	80
Noninvasive	6	0.0	0.0	0	0

invasiveness. Invasive tumors ($n=44$) had a significantly higher mean CPS of 20.07 ($\pm$27.07), with scores ranging from 0 to 80, while all noninvasive tumors ($n=6$) had a CPS score of 0 (Fig. 2 a and b). These results support a potential link between higher PD-L1 expression and tumor aggressiveness and invasiveness, which could be important when assessing the activity for PD-1/PD-L1-targeted immunotherapy (Bellmunt et al. 2017).

As shown in Table 4, both ANOVA and Kruskal–Wallis tests demonstrate a highly significant variation in CPS across various tumor grade categories. The one-way ANOVA confirmed a substantial overall effect ($F=76.24$, $p=1.77\times10^{-15}$), suggesting that at least one grade group has a mean CPS that differs from the others. This is supported by the Kruskal–Wallis test ($H=20.67$, $p=3.24\times10^{-5}$).

Hematoxylin and eosin (H&E)-stained sections were examined to show irregular and papillary protrusions of epithelial cells, pleomorphism, architectural disorder, an increased nucleus-to-cytoplasm ratio, and hyperchromatic nuclei, indicating malignant epithelial cell proliferation (Fig. 3). IHC staining was evaluated to confirm the overexpression of a specific PDL-1 protein (Fig. 4).

Discussion

Including both transurethral resection and cystectomy specimens may introduce heterogeneity. However, this approach enabled assessment of PD-L1 expression across

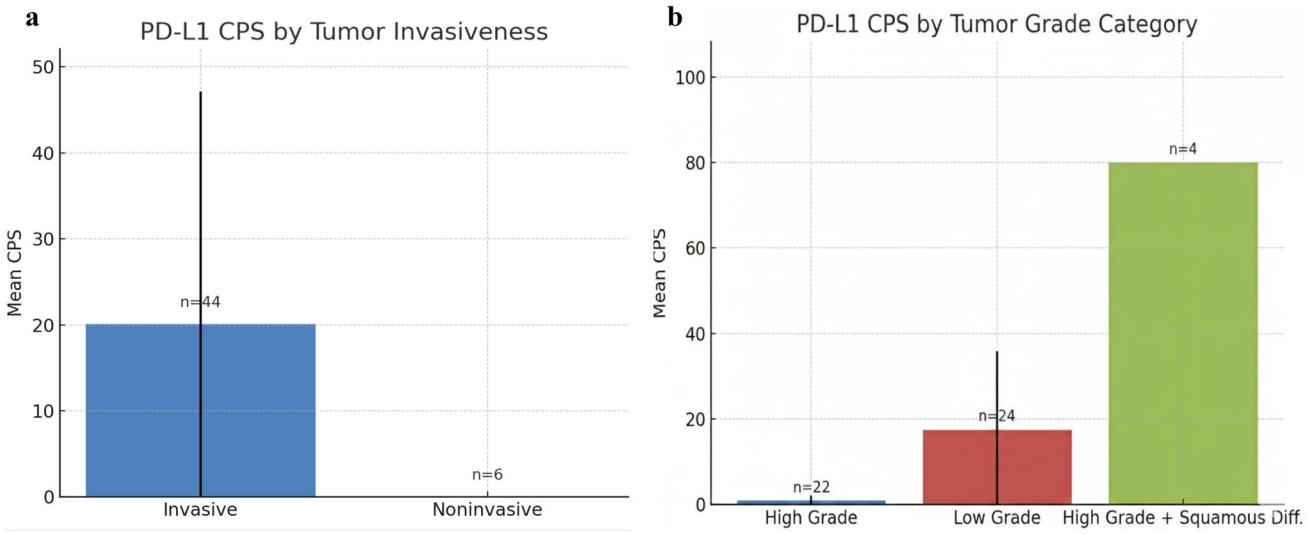

Fig. 2 **a** CPS scores associated with tumor invasiveness; **b** CPS scores associated with tumor grade

Table 4 ANOVA and Kruskal–Wallis tests

Test	Statistical analysis	*p*-value
ANOVA	76.24	1.77×10^{-15}
Kruskal–Wallis	20.67	3.24×10^{-5}

disease stages and invasion levels (Khalil et al. 2025; Jong et al. 2021). Future studies with stratified analyses and larger cohorts based on specimen type are recommended to validate these findings further. Many historical and recent observations hypothesized that there is host immunity modulation in bladder cancer pathogenesis since there was acquired immune dysfunction was reported in many cases of high-grade tumors of bladder cancer, in addition to the highest response of these tumors to immunotherapy in non-muscle-invasive UC (Inman et al. 2007). This finding aligns with a previous study reported by Heabah and Bedeer (Heabah and Bedeer 2021), which confirmed that PD-L1 expression is not highly affected by sex in UC. These results imply that male and female patients might exhibit similar responses to PD-1/PD-L1-targeted immunotherapy, supporting the gender-neutral use of immune checkpoint blockade in clinical settings. In this retrospective study of 50 FFPE tissue samples PD-L 1 membranous expression was expressed in 17 cases (33.3%), that was consistent with study performed by Al Nabhani et al. (Al Nabhani et al. 2022) who found that 19/63 (30.2%) were PDL-1 positive, as well as in this study found the most UC cases occurred in male patients at percentage of 80.4%, that was reported at nearly percentage of (86.21%) for male patients in a previous study in north of Iraq performed in Duhok (Mustafa et al. 2024).

In routine practice, many pathologists often classify invasive UC as high grade, even when low-grade papillary morphology is present. In fact, urologic pathologists in the UC typically grade nearly all invasive UC as high-grade. Additionally, most morphologically low-grade invasive UC represent specific histological variants, such as nested, microcystic, plasmacytoid, or tubular types. When these variants are excluded, truly low-grade invasive carcinomas are rare (Tian and Epstein 2015; Singh et al. 2024). In the current study, tumor grading was performed strictly based on morphological criteria, regardless of invasion status. While invasive UC is often graded as high grade in routine practice, grading relied solely on cytological and architectural features. Consequently, a limited number of tumors retained low-grade morphology despite demonstrating stromal invasion.

Secondly, a notable pattern appears when analyzing PD-L1 expression concerning histological subtype and tumor grade. Low-grade tumors had a significantly higher CPS compared to high-grade tumors. This result is contradictory to the previous report linking high-grade tumors to elevated PD-L1 expression due to increased mutational burden and immunogenicity (Mino-Kenudson 2016). However, these differences may be due to the specific subtype of the high-grade tumors included in this study. Among the high-grade tumors, tumors with squamous differentiation showed high and consistent CPS scores, suggesting that squamous differentiation may be a better predictor of PD-L1 overexpression than tumor grade alone. This agreed with the findings of Gulmann et al. (2013), who observed that squamous differentiation in squamous cell carcinoma is often associated with immune evasion strategies (expression of PD-L1) and more aggressive behavior. In a previous study, a high PDL-1 expression was observed

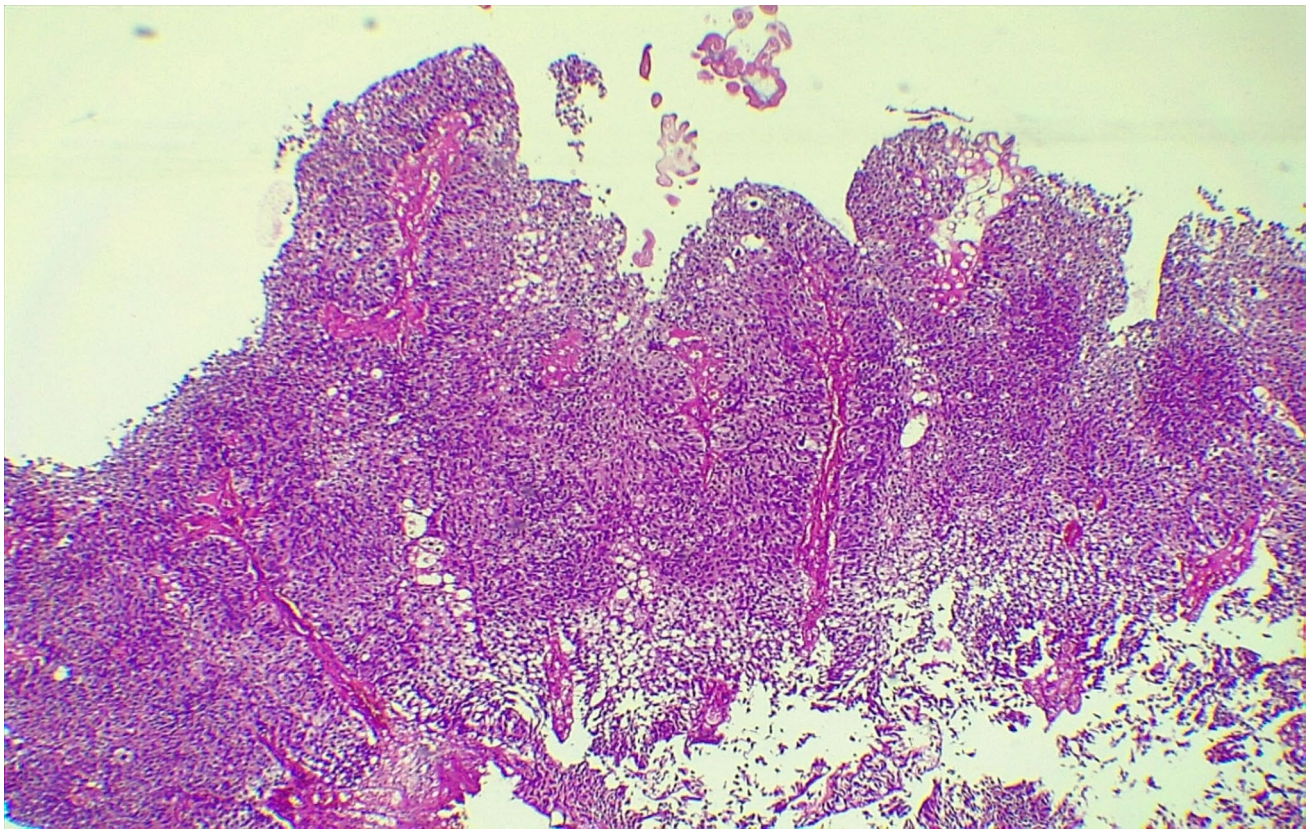

Fig. 3 Hematoxylin and eosin stain (4X) invasive high-grade papillary urothelial carcinoma

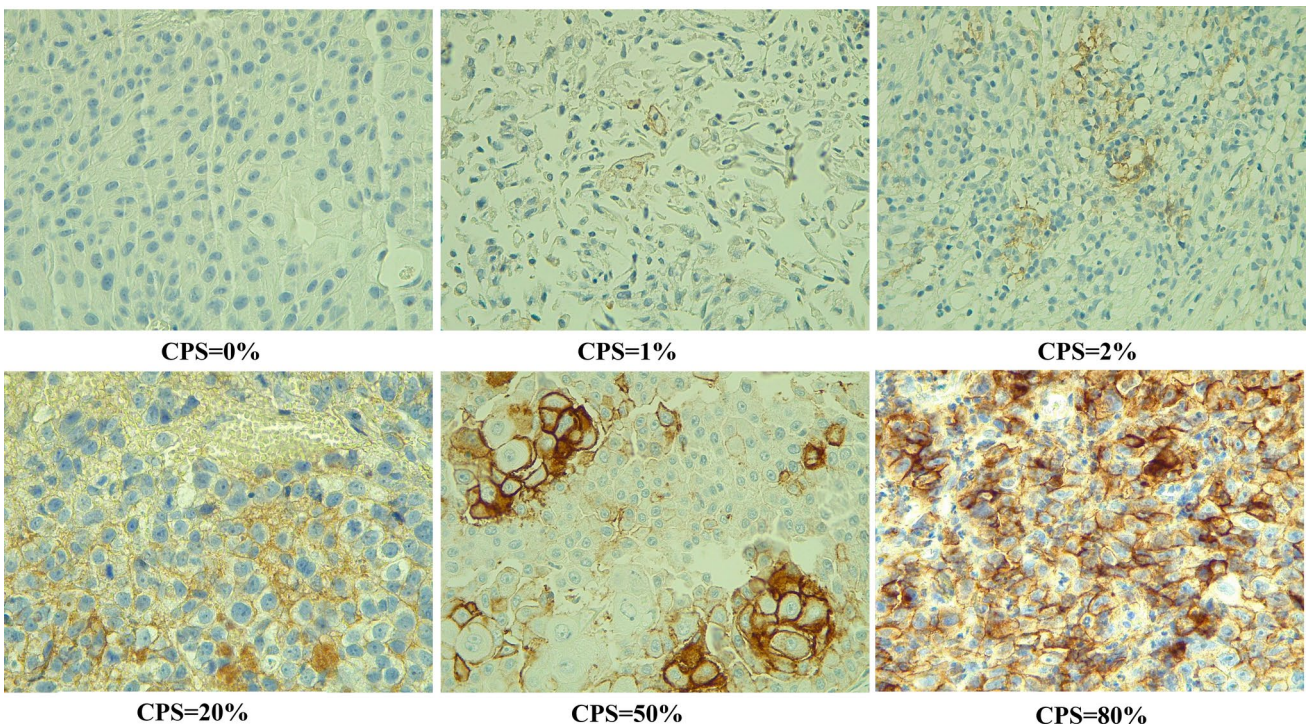

Fig. 4 PD-L1 expression in urothelial carcinoma tissues at various CPS levels: 0, 1, 2, 20, 50, and 80%. The intensity and extent of PD-L1 staining progressively increase with higher CPS values, indicating greater positivity in immune cells and the tumor

in high-grade tumors, this finding was seen in previous studies in high-grade tumors such as a study of Kawahara et al. (2018), potential contributing factors to this observation include the utilization of different clones, nature of high-grade carcinomas, tumor heterogeneity, and the varied cut-offs for positivity (Kumar et al. 2022).

The current study also showed a strong correlation between tumor invasiveness and PD-L1 expression. All noninvasive tumors had a CPS of 0, while invasive tumors showed a significantly higher CPS of 20.07 (±27.07). This finding supports the hypothesis that PD-L1 upregulation plays a critical role in immune escape during tumor progression (Tagayasu et al. 2025). The result demonstrated by Dong et al. (2002) agreed with the finding that reported PD-L1 expression enhances tumor immune evasion by inducing T-cell apoptosis. In contrast, Massari et al. (2018) reported the role of PD-L1 in UC, especially in invasive forms, with the absence of PD-L1 expression in noninvasive tumors. Further reinforcing the idea that PD-L1 supports tumor aggressiveness and serves as a marker of disease progression. Reis et al. (2019) reported different percentages of positive expression samples of PD-L1 with different cut-offs, they reported that a 1% total cell reactivity cut-off was applied, (54%) of samples were PD-L1 positive, while when the cutoff was set to 5%, there was a reduction in the mean number of positive cases to (37%). While (Feng et al. 2019) reported that non significant relation was seen between PD-L1 expression and higher grade of tumors.

ANOVA analysis and Kruskal–Wallis tests showed the significant CPS differences between tumor grades ($p < 0.001$), confirming that PD-L1 expression varies significantly across different pathological groups. This result confirmed the role of CPS as a robust biomarker in the classification of UC. Bellmunt et al. (2017) and Powles et al. (2014) reported the role of PD-1/PD-L1 inhibitors in patients with PD-L1-positive tumors. Therefore, including the CPS test in routine diagnostic and prognostic workflows will enhance chemotherapy strategies to be more effective for patient treatment. Regarding muscle invasion, there was a significant difference in the PDL-1 expression between muscle-invasive and non-muscle invasive UB cancer, which was consistent with Gupta et al. (2022) and Ibrahim et al. (2023) who reported that a significant association exists between high PDL-1expression and muscular invasion.

Conclusion

In conclusion, this study indicates that PD-L1 expression (assessed by CPS) is closely associated with specific pathological features of urothelial carcinoma, such as invasiveness and histological subtype. These associations may have an important effect on immunotherapy and may help to discover an effective treatment approach for bladder cancer. The current study searched the expression patterns of PD-L1 in UC and their association with clinicopathological features (gender, grade, tumor, histological subtype, and invasiveness). The results showed the role of PD-L1 as a biomarker for immune checkpoint inhibitor therapy in bladder cancer. Importantly, the results revealed no statistically significant difference in PD-L1 expression between female and male patients, as measured by the CPS. Several limitations encumbered this study; first, it was a retrospective analysis in relatively few samples, in addition to selection bias, which can result since the specimens were obtained via trans urothelial resection. Second, the underlying mechanisms of bladder cancer development were not assessed, although there was a difference between low- and high-grade cancers in the expression of PDL-1. Further studies are required, as there are no prior studies in Basrah regarding this subject.

Author contributions Z.A.M.: Data collection, literature review, and initial manuscript drafting, O.F.H.: Methodology design, histopathological analysis, and data interpretation, and H.A.H.: Conceptualization, supervision, critical manuscript revision, and final approval of the version to be published.

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Data availability The datasets generated and/or analyzed in the current study are available from the corresponding author (H.A.H.) on reasonable request.

Declarations

Statement of ethics This study protocol was reviewed and approved by the University of Basrah, College of Dentistry, approval number [BDC-6-06-24-9].

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication Consent for publication was obtained for every individual person's data included in the study.

Conflict of interest The authors declare no competing interests.

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