RESEARCH ARTICLE

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Exploring the Role of CD155 in Urothelial Carcinoma of the Urinary Bladder: An Immunohistochemical Study & Its Correlation With *PD-L1*

Passant Essam Shibel[1], Aya Magdy Elyamany[1]*, Galal El Shorbagy[2], Eman Ahmed Abd Elmaogod[3]

Abstract

Background: Urinary bladder carcinoma is one of the most immunogenic cancers. Several immune checkpoint inhibitors targeting programmed death-ligand 1 (*PD-L1*) have been approved by the FDA for bladder carcinoma treatment. However, additional immunotherapeutic targets are still needed. *CD155* is another immune checkpoint molecule that has been shown to be overexpressed in several cancers and is associated with poor prognosis. **Aim:** This study aimed to evaluate *CD155* expression in cases of urinary bladder urothelial carcinoma using immunohistochemistry and to correlate this expression with the clinicopathological parameters of the cases as well as with *PD-L1* expression. **Methods:** Immunohistochemical staining for *CD155* and *PD-L1* was performed on 67 cases of urothelial carcinoma of the urinary bladder. **Results:** *CD155* was positive in 41.8% of cases and was significantly associated with invasive tumors and advanced T stage. *PD-L1* was positive in 35.8% of cases and was significantly associated with advanced T stage, distant metastasis, muscle invasion and lymphovascular emboli. A statistically significant positive correlation was observed between the expression of both *CD155* and *PD-L1*. **Conclusion:** Our study demonstrated increased expression of *CD155* in urothelial carcinoma of the urinary bladder with advancing stage, suggesting its potential as a therapeutic target. Additionally, *CD155* expression correlated positively with *PD-L1* expression, indicating that some patients might benefit from a combined blockade of both targets.

Keywords: Urinary bladder – Urothelial carcinoma – *CD155* – *PD-L1* – Immunohistochemistry

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Introduction

Worldwide, bladder cancer (BC) ranks as the tenth most common cancer [1]. In Egypt, urinary bladder cancer is the most prevalent cancer in males (16%) and the second most common cancer in females (12%), leading to more than 7900 deaths per year, which is considerably higher than most other parts of the world [2].

Radical cystectomy (RC) with pelvic lymph node dissection is indicated for patients with muscle-invasive BC and those with Bacillus Calmette-Guerin (BCG)-resistant non-muscle invasive BC [3]. Unfortunately, up to 40% of patients experience lymph node or distant metastases within five years post-operative [4]. For a better prognosis, maintenance chemotherapy has been considered [5], however; not all patients respond well to such anti-cancer drugs; additionally, treatment-related adverse events were recorded [6].

Nowadays, immunotherapies have been introduced into the treatment of various cancers including bladder carcinoma. Bladder urothelial carcinoma is known to be highly immunogenic, where it shows one of the highest mutational burdens among different cancers and is characterized by relatively high *PD-L1* expression. Immunotherapy by intravesical BCG has been used in superficial bladder carcinoma treatment for decades. Lately, two *PD-1* targeting antibodies (nivolumab and pembrolizumab) and three *PD-L1* targeting antibodies (avelumab, atezolizumab, and durvalumab) have been FDA approved for treatment of metastatic urinary bladder carcinoma [7].

Despite such advances, obstacles regarding resistance to immune checkpoint inhibitors (ICIs), whether primary or acquired, appeared. Thus, additional targets are needed while considering the possibility of ICI combination therapy to attain synergetic effects with improved clinical outcomes [8].

Cluster of differentiation 155 (*CD155*) is a transmembrane protein, initially described as a poliovirus receptor (PVR). It functions as a ligand for three

*[1]Department of Anatomic Pathology, Faculty of Medicine, Cairo University, Egypt. [2]Department of Urology, Faculty of Medicine, Cairo University, Egypt. [3]Department of Anatomic Pathology, Faculty of Medicine, Beni-Suef University, Egypt. *For Correspondence: aya.magdy@kasralainy.edu.eg*

receptors; DNAX-associated molecule 1 (DNAM- 1), T-cell immunoglobulin and ITIM domain (TIGIT), and CD96 receptors, which are expressed on the surface of natural killer and T-cells [9]. *CD155* is scarcely expressed in normal tissues, yet it is overexpressed in numerous carcinomas including breast [10, 11], lung [12], ovarian [13], and prostate [14], where it has been shown to be an unfavorable prognostic marker [15].

Regarding its immune function, *CD155* can act as both an immunostimulant when interacting with DNAM-1 (CD226) and an immunosuppressant when interacting with TIGIT or CD96. However, *CD155* has been shown to have the highest affinity for TIGIT, thus it tends to suppress the activity of TIGIT expressing NK and T cells in the tumor microenvironment. *CD155* blockade has been shown to augment tumor directed immunity [16].

In addition to its immune functions, *CD155* has been shown to favor angiogenesis, as well as tumor cell migration and proliferation by upregulating some cell cycle regulators such as cyclins D2 and E [17, 18].

Studies have reported enhanced anti-tumor effect when combining anti- *CD155* and anti- *PD-L1* therapies. Using a bispecific antibody targeting both *CD155* and *PD-L1*, Ma et al. [19] reported synergistically enhanced T cell function. Mao et al. [20] using a transgenic mouse model reported that combined blockage of *CD155* and *PD-L1* promoted the generation of effector T cells and inhibited tumor cell proliferation . Additionally, Kawashima et al. [21] concluded that TIGIT/*CD155* axis may mediate resistance to ICIs in melanoma cases, suggesting that TIGIT blocking therapies can significantly improve response to ICIs.

Our study aimed at evaluating *CD155* expression by immunohistochemistry in urinary bladder urothelial carcinoma to detect the potentiality of targeting it as cancer immunotherapy. We also correlated *CD155* expression with the clinico-pathological parameters of the tumors and with *PD-L1* expression.

Materials and Methods

Retrieval of Cases

This cross-sectional study was performed on 67 formalin fixed, paraffin embedded blocks of bladder urothelial carcinoma, obtained from the archives of Pathology department, Kasr Al-Ainy hospital at Cairo University from January 2021 to December 2022. Approval of research ethical committee at faculty of Medicine, Cairo University (approval code: N-413-2023) was obtained before starting.

Calculation of sample size was performed using statcalc program of EPI-info version 7.2 according to the following parameters: the proportion of the outcome (positive expression of *CD155* in urothelial carcinoma) was 21.4% [17], acceptable margin of error was 10%, confidence level was 95% and design effect was 1. The minimum calculated required sample size was 65 cases.

Inclusion criteria included cases of urothelial carcinoma of any age and sex, performing either cystoscopic biopsy or radical cystectomy. Exclusion criteria included specimens with inadequate tumor tissue, extensive cautery artifact, crushing or wide necrosis, cystoscopic biopsy specimens free of muscularis propria were also excluded.

For each case, the data obtained from the pathology requests and reports included age and sex of patient, presence of distant metastasis and lymph node (LN) metastasis for cases performing radical cystectomy with lymph node dissection. Pathological T staging was accomplished according to the 8th edition (2017) of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual [22]. For further statistical evaluation, T stage was further categorized into early (T1 & T2) and late (T3 & T4) [17].

Histopathological Examination

For each case, a routine Hematoxylin and Eosin (H&E) stained section was prepared for histopathological examination and two sections were cut on charged slides for immunostaining.

The tumors were histologically graded and classified according to the latest World Health Organization (WHO) recommendations [23]. The presence of lympho-vascular emboli (LVE) and associated Schistosomal infestation were also evaluated.

Tumor Infiltrating Lymphocytes (TILs) Assessment

Scoring of Tumor Infiltrating Lymphocytes for each case was performed following the International Immuno-Oncology Biomarker Working Group recommendations [24]. Only lymphocytes and plasma cells in the invasive tumor stroma and tumor invasive edge were evaluated; neutrophils and eosinophils were excluded. Lympho-plasma cells within the cores of the non-invasive papillary structures, in areas of necrosis and crushing were all excluded from the scoring. Tumor infiltrating lymphocytes were reported as the percentage of stromal area occupied by lympho-plasma cells and not as percentage of stromal cells [24]. As the working group didn't set clinically valid cut points for TILs stratification, our cases were stratified into Low TILs (<30%) and High TILs (≥30%) [25].

CD155 & PDL-1 Immunohistochemical Staining & Evaluation

Immunostaining was performed using an automated immunostainer; BenchMark XT (Ventana) autostainer. The used primary antibodies were anti-*CD155* (D8A5G) monoclonal antibody (#81254: Cell Signaling Technology; Danvers, MA, USA) and anti- *PD-L1* (CD274) monoclonal antibody (#abx236281: Abbexa LTD, Cambridge, UK).

CD155 staining was detected in the tumor cell membrane. Each case was offered an immunoreactivity (IR) score obtained by multiplying the staining intensity score and percentage of positive tumor cells score. Staining intensity was scored as follows: 0: negative, 1: weak, 2: moderate and 3: strong. The percentages of positive tumor cells were scored as follows: 0: no staining, 1: <25%, 2: 25%-50%, 3: 50%-75% and 4: >75%. An IR score of two or above was considered positive [11].

PD-L1 staining was also detected in the tumor cell membrane and in both the cell membrane and cytoplasm

of TILs. A combined positivity score (CPS) was obtained for each case, which is defined as the total number of *PD-L1*-positive (tumor and immune) cells divided by the total number of viable tumor cells and then multiplied by 100. Cases with CPS of ≥ 10 were considered *PD-L1* positive [26].

Statistical Analysis

The data was transferred to SPSS Software program, version 25 for statistical analysis. Quantitative data (age) was expressed using mean and standard deviation while frequencies were used for qualitative data. The association between the categorical variables was estimated using the chi-square test. P value of < 0.05 was considered as statistically significant.

Results

The age in our study ranged between 35 and 81 years with a mean age of 59.78 years. Most of our cases were males (91%). Among the studied cases, 23.9% were non-invasive carcinomas while 76.1% were invasive carcinomas, 20.9% were low grade and 79.1% were high grade. Regarding T stage, 55.2% of the cases were early (T1 & T2) and 44.8% were late (T3 & T4). Lymph node metastasis was detected in 7/23 cases who were subjected to lymph node dissection. Distant metastasis was detected in 14.9% of the studied cases.

Muscle invasion, LVE and associated bilharzial infestation were documented in 53.7%, 43.3% and 23.9% of our cases respectively. High TILs (>30%) were detected in 20.9% of cases. The pathological characteristics of the cases are presented in Table 1.

Expression of CD155 & PDL-1 and their correlation with the clinico-pathological parameters of the cases

CD155 was considered positive in 41.8% of the cases (Figure 1) and showed statistically significant higher expression in invasive carcinoma cases when compared to non-invasive cases (p value =0.032). Additionally, *CD155* expression showed a statistically significant direct correlation with advanced T stage (p value =0.026). *CD155* expression was also associated with high grade, muscle invasion, LVE, high TILS, associated bilharzial infestation and distant metastasis, yet absence of lymph node metastasis (Figure 2). However, none of those correlations showed significant differences.

PD-L1 was considered positive in 35.8% of the studied cases and showed statistically significant correlation with advanced T stage (p value =0.029), distant metastasis (p value =0.015), muscle invasion (p value =0.009) and lymphovascular emboli (p value =0.018). *PD-L1* expression was also associated with high grade, high TILS, associated bilharzial infestation and absence of lymph node metastasis. However, none of those correlations showed significant differences. *PD-L1* immunohistochemical expression was represented in Figure (3).

The correlations of *CD155* and *PDL-1* expression with various clinico-pathological characteristics of the studied cases are summarized in Table 2. A statistically significant direct correlation was also detected in our study between the expression of both *CD155* and *PD-L1* (p value =0.040) (Table 3).

Table 1. Clinico-Pathological Parameters of the Studied Cases

Parameters	N (%)
Age	
< 60 y	33 (49.3%)
≥ 60 y	34 (50.7%)
Sex	
Male	61 (91%)
Female	6 (9%)
Invasion	
Non-invasive carcinoma	16 (23.9%)
Invasive carcinoma	51 (76.1%)
Muscle invasion	
Absent	31 (46.3%)
Present	36 (53.7%)
Histologic grade	
Low	14 (20.9%)
High	53 (79.1%)
T stage	
Early	37 (55.2%)
Advanced	30 (44.8%)
Lymph Node metastasis	
Absent	16 (23.9%)
Present	7 (10.4%)
Could not be assessed (lymphadenectomy was not performed)	44 (65.7%)
Distant metastasis	
Absent	57 (85.1%)
Present	10 (14.9%)
Lymphovascular invasion	
Absent	38 (56.7%)
Present	29 (43.3%)
TILs	
Low	53 (79.1%)
High	14 (20.9%)
Bilharziasis	
Absent	51 (76.1%)
Present	16 (23.9%)

Discussion

The clinical success of immune checkpoint targeting therapies, including those targeting *PD-1* and *PD-L1*, has encouraged searching for additional immunotherapeutic targets and considering the possibility of combined immunotherapies. *CD155* may represent one of these targets, owing to its detected immunosuppressive function and association with poor prognosis in several cancers [16].

Our study investigated the expression of *CD155*

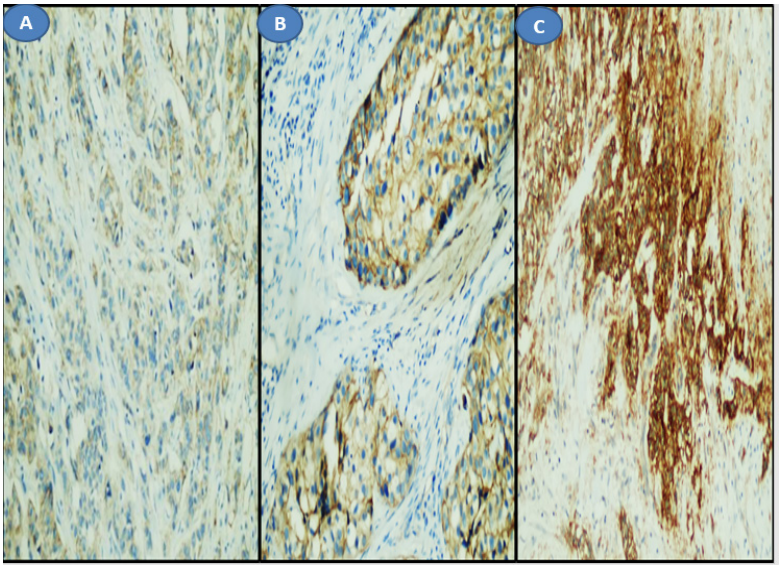

Figure 1. Different Intensities of *CD155* Membranous Immunohistochemical Expression in Urothelial Carcinoma of the Urinary Bladder: (A) Weak expression (x200 original magnification). (B) Moderate expression (x200 original magnification). (C) Strong expression (x200 original magnification).

Table 2. Correlation of *CD155* and *PDL-1* Expression with Clinicopathological Characteristics among the Studied Cases

Parameter	CD155		P value	PD-L1		P value
	Positive 28 (41.8%)	Negative 39 (58.2%)		Positive 24 (35.8%)	Negative 43 (64.2%)	
Invasion			0.032*			0.103
Non-invasive carcinoma	3 (18.8%)	13 (81.3%)		3 (18.8%)	13 (81.3%)	
Invasive carcinoma	25 (49%)	26 (51%)		21 (41.2%)	30 (58.8%)	
Muscle invasion			0.142			0.009*
Absent	10 (32.3%)	21 (67.7%)		6 (19.4%)	25 (80.6%)	
Present	18 (50%)	18 (50%)		18 (50%)	18 (50%)	
Histologic grade			0.082			0.59
Low	3 (21.4%)	11 (78.6%)		2 (14.3%)	12 (85.7%)	
High	25 (47.2%)	28 (52.8%)		22 (41.5%)	31 (58.5%)	
T stage			0.026*			0.029*
Early (T1&T2)	11 (29.7%)	26 (70.3%)		9 (24.3%)	28 (75.7%)	
Advanced (T3&T4)	17 (56.7%)	13 (43.3%)		15 (50%)	15 (50%)	
Lymph node metastasis			0.554			0.062
Absent	9 (56.2%)	7 (43.8%)		9 (56.2%)	7 (43.8%)	
Present	3 (42.9%)	4 (57.1%)		1 (14.3%)	6 (85.7%)	
Distant metastasis			0.568			0.015*
Absent	34 (59.6%)	23 (40.4%)		17 (29.8%)	40 (70.2%)	
Present	5 (50%)	5 (50%)		7 (70%)	3 (30%)	
LVE			0.15			0.018*
Absent	25 (65.8%)	13 (34.2%)		9 (23.7%)	29 (76.3%)	
Present	14 (48.3%)	15 (51.7%)		15 (51.7%)	14 (48.3%)	
TILs			0.928			0.537
Low	31 (58.5%)	22 (41.5%)		18 (34%)	35 (66%)	
High	8 (57.1%)	6 (42.9%)		6 (42.9%)	8 (57.1%)	
Bilharziasis			0.445			0.448
Absent	31 (60.8%)	20 (39.2%)		17 (33.3%)	34 (66.7%)	
Present:	8 (50%)	8 (50%)		7 (43.8%)	9 (56.3%)	

* Statistically significant

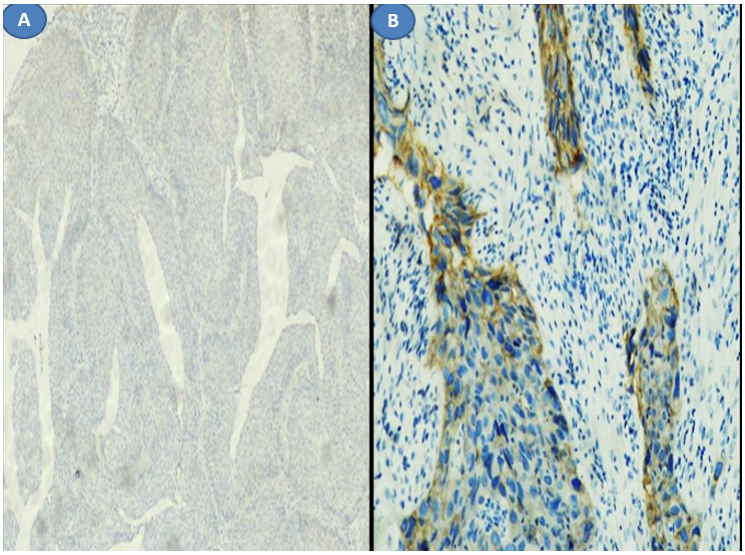

Figure 2. A: Negative *CD155* expression in low grade non-invasive papillary urothelial carcinoma of the bladder with low tumor infiltrating lymphocytes (x100 original magnification). B: Positive *CD155* membranous immunohistochemical expression in high grade invasive urothelial carcinoma with high tumor infiltrating lymphocytes (x200 original magnification).

Table 3. Correlation between *PDL-1* Expression and *CD155* Expression in the Studied Cases

		CD155		P Value
		Negative	Positive	
PD-L1	Negative	29 (67.4%)	14 (32.6%)	0.040*
	Positive	10 (41.7%)	14 (58.3%)	

and *PD-L1* by immunohistochemistry in 67 cases of urinary bladder urothelial carcinoma, either performing cystoscopic biopsies or radical cystectomies and correlated such expression with the clinico-pathological parameters of the studied cases. We also studied the relation between *CD155* and *PD-L1* expression in our cases as a primary step in detecting the possibility of combining *CD155* and *PD-L1* targeting therapy.

We detected *CD155* expression in 41.8% of our cases. Although *CD155* immunohistochemical expression in urothelial carcinoma was not extensively investigated in the literature, our figure was close to the results of Zhang et al., 2020 who reported *CD155* expression in 49.5% of their cases, using the same antibody clone as in our study, yet it worth mentioning that they only studied non-metastatic muscle invasive cases [27]. Another study conducted by Mori et al. [17] revealed *CD155* expression in 21.3% and 23.3% of urinary bladder urothelial carcinoma cases when considering membranous and cytoplasmic staining respectively. While studying *CD155* expression

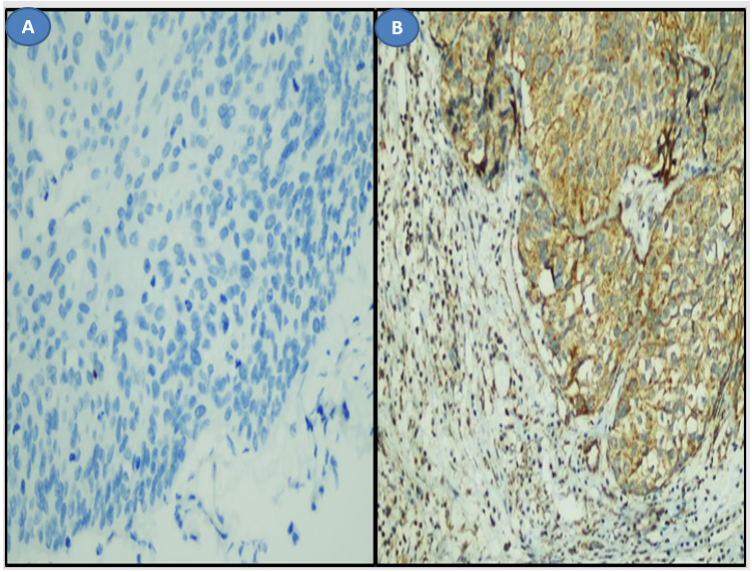

Figure 3. A: Negative *PD-L1* expression (tumor cells & immune cells) in low grade non-invasive papillary urothelial carcinoma of the bladder with low tumor infiltrating lymphocytes (x200 original magnification). B: Positive *PD-L1* immunohistochemical expression (cell membrane of the tumor cells and both the cell membrane and cytoplasm of immune cells) in high grade invasive urothelial carcinoma with high tumor infiltrating lymphocytes (x200 original magnification).

in upper urinary tract urothelial carcinoma, Ikeda et al. [28] detected 85.1% positive cases, yet they considered cytoplasmic staining for positivity .

Such differences in the reported figures may be attributed to various factors including the used antibody clones, using full-face sections or tissue microarrays, the cut-offs used for positivity, considering membranous or cytoplasmic staining for positivity and features of the studied population itself (e.g., all stages versus muscle invasive, metastatic versus non-metastatic, etc.).

In our study, *CD155* showed significantly higher expression in invasive rather than non-invasive carcinoma cases and in advanced stage (T3 and T4) rather than early stage (T1 and T2) cases. Additionally, higher expression was detected in muscle invasive than non-muscle invasive cases, yet with no achieved statistical significance; our results thus suggested a role for *CD155* in urothelial carcinoma progression.

Our results agreed with Ikeda et al. [28] who detected the lowest *CD155* expression in Ta (non-invasive) upper urinary tract urothelial carcinoma cases compared to other invasive stages and they also detected statistically significant higher *CD155* expression with advancing stages. Mori et al. [17] similarly detected statistically significant higher *CD155* expression in higher stage cases, only when considering membranous but not cytoplasmic *CD155* expression .

The association of *CD155* expression with advanced T stage was generally supported by several studies in the literature including those studying urinary bladder carcinoma [27] and others including breast carcinoma [10] and cholangiocarcinoma [29]. Additionally, a meta-analysis including cancers of various organs detected significantly higher *CD155* expression in advanced tumor stage cases [16].

CD155 showed higher expression in high compared to low grade cases in our study; a finding showing wide agreement in the literature including studies performed on urinary bladder carcinoma [27, 17], breast carcinoma [30], cholangiocarcinoma [29] and non-small cell lung carcinoma (NSCLC) [31].

Although our study detected higher *CD155* expression in LVE positive cases and in cases with distant metastasis, we detected a contradictory higher *CD155* expression in lymph node negative cases; such a finding may be explained by the relatively small number of cases performing lymph node dissection in our study.

In agreement with our results, Zhang et al. [27], Ikeda et al. [18] and Mori et al. [17] detected higher *CD155* expression in LVE positive cases, yet all of them detected higher *CD155* expression in LN metastatic cases. Interestingly, a study performed on NSCLC cases suggested that *CD155* expression correlated with vascular rather than lymphovascular invasion [31]. In the literature, *CD155* expression was associated with lymph node metastasis in breast carcinoma [10], cholangiocarcinoma [29] and gastric carcinoma [32].

Although, to our knowledge, none of the studies in the literature correlated *CD155* immunohistochemical expression to distant metastasis in urothelial carcinoma, studies performed on other organs detected higher *CD155* expression in metastatic cases in lung adenocarcinoma [12] and gastric carcinoma [32]. The association of *CD155* expression with lymph node and distant metastasis was also supported by a meta-analysis involving cancers of different organs [16].

One possible limitation of our study is that we assessed tumor infiltrating lymphocytes using H&E staining, without further stratification using immunophenotyping, however we detected higher *CD155* expression in high TILs cases, yet with no statistical significance. Although such a relation was not studied previously in urothelial carcinoma to our knowledge, studies addressing such relation showed conflicting results. While a study performed on breast carcinoma showed a statistically significant direct relation of *CD155* with TILs [30], other studies performed on pancreatic carcinoma and ovarian high grade serous carcinoma conversely showed a negative correlation between *CD155* expression and stromal TILs [33, 13]. Studying the different sub-populations of TILs separately could clarify such conflicting results.

In our study, *PD-L1* expression was detected in 35.8% of our cases; although invasive cases showed higher expression than non-invasive cases, such relation didn't reach statistical significance. This agreed with Bellmunt et al. [34] who reported no difference in *PD-L1* expression between non-invasive and invasive urothelial carcinoma cases.

PD-L1 expression was significantly associated in our study with advanced T stage, presence of muscle invasion, lymphovascular emboli and distant metastasis. *PD-L1* expression in urothelial carcinoma has been widely reported to be a poor prognostic factor, usually associated with muscle invasion [35, 36] and higher T stage [37].

Finally, we detected a statistically significant direct correlation between *CD155* and *PD-L1* CPS, where 14 of our cases (about 20%) co-expressed *CD155* and *PD-L1*. Although, Mori et al. [17] detected no statistical correlation between *CD155* and *PD-L1* expression either on tumor or immune cells in their studied urinary bladder urothelial carcinoma cases, our finding agreed with studies correlating the expression of *CD155* and *PD-L1* in upper tract urothelial carcinoma [28] and esophageal carcinoma [38].

A study conducted on triple negative breast carcinoma (TNBC) showed a significant correlation of *CD155* expression with *PD-L1* expression on TC but not IC [39]. Similarly, others reported significant *CD155* expression with TC *PD-L1* expression in TNBC [9], NSCLC [31, 40], cutaneous squamous cell carcinoma [41] and gall bladder carcinoma [42].

One limitation of our study is the lack of data regarding patient's survival and cancer related morbidity.

In conclusion, our study detected increased expression of *CD155* in urinary bladder urothelial carcinoma cases and an association of such expression with invasion and advancing stage, highlighting *CD155* as a promising therapeutic target. Additionally, *CD155* correlated positively with *PD-L1* expression in our cases, highlighting a subset of cases that co-express both biomarkers and can be candidates for combined blockade of both immune checkpoints.

Author Contribution Statement

All authors shared in research design and approval of the manuscript. Research design: PES, AME, GE and EAA; data collection: PES, AME, GE and EAA; data interpretation: PES and AME; statistical analysis: PES; writing of the manuscript: PES, AME, and EAA; work revision and final approval: PES, AME, GE and EAA.

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Ethical approval

The Faculty of Medicine's Ethical Committee at Cairo University approved this work (Ethical approval code: N-413-2023).

Availability of data and material

The dataset generated in the current study is available from the corresponding author on demand. This work is not a part of student thesis and not registered in any registration dataset.

Conflict of interest

The authors declare that they have no conflict of interest.

List Of Abbreviation

AJCC: American Joint Committee on Cancer's
BC: Bladder cancer
BCG: Bacillus Calmette-Guerin
ICIs: immune checkpoint inhibitors
CD155 : Cluster of differentiation
CPS: Combined positivity score
DNAM- 1: DNAX-associated molecule 1
FDA: Food and Drug Administration
IR: Immunoreactivity score
LN : Lymph node
LVE: Lympho-vascular emboli
NSCLC: Non-small cell lung cancer
PD-L1: Programmed death - ligand 1
PVR: Poliovirus receptor
TIGIT: T-cell immunoglobulin and ITIM domain
TILs: Tumor Infiltrating Lymphocytes
TNBC: Triple negative *CD155* breast carcinoma

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