

IL1RL2 is related to the expression and prognosis of bladder cancer

XUEMEI HA^{1,2*}, YUE LI^{3*}, ZIHUI GAO^{1,2}, JIAZHAO CUI^{1,2}, YUZHU NIE^{1,2}, LIHUA SUN^{1,2} and WENZHI GAO^{1,2}

¹Department of Pathology, Peking University First Hospital-Miyun Hospital, Beijing 100034, P.R. China;

²Miyun Teaching Hospital, Capital Medical University, Beijing 100034, P.R. China; ³Department of Urology, The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei 050000, P.R. China

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Abstract. IL1RL2 has been reported to be highly expressed in a variety of tumor types whereas its role in bladder cancer (BLCA) remains unclear. The aim of the present study was to explore the prognostic value of IL1RL2 in BLCA and its relationship with clinical pathological features. The Cancer Genome Atlas (TCGA) database was used to assess the levels of IL1RL2 expression in BLCA tissues and cells, which were validated by reverse transcription-quantitative polymerase chain reaction and western blotting. Immunohistochemistry was employed to analyze expression of the IL1RL2 gene in 17 pairs of tumor and normal specimens, as well as 112 samples with different stages and grades of tumors. To investigate the biological functions of IL1RL2 in BLCA, co-expression networks and functional enrichment analyses were conducted. A protein-protein interaction network was constructed using interaction gene search tools. IL1RL2 was revealed to be clearly expressed in BLCA cells and tissues. The area under the curve for amplification of IL1RL2 distinguishing between tumor and normal tissues was 0.700 (95% CI: 0.579-0.821) in the TCGA database and 0.647 (95% CI: 0.497-0.797) in Miyun chart database, respectively. Furthermore, in our database, both univariate and multivariate analyses indicated that IL1RL2 expression was an independent risk factor for overall survival (OS). Kaplan-Meier survival analysis revealed an association between high IL1RL2 expression and low OS. Pathway enrichment analysis suggested that IL1RL2 is involved in the regulation of tumor progression through the MAPK signaling

pathway. The expression level of IL1RL2 was associated with the stage, grade, lymph node album and prognosis of BLCA.

Introduction

Bladder cancer (BLCA) is the most common malignancy of the genitourinary system in China and ranking tenth worldwide (1-3). BLCA is classified into non-muscular-invasive BLCA (NMIBC) and muscle-invasive BLCA (MIBC). NMIBC, which accounts for 75% of BLCAs, progresses slowly and has a long survival, however it still develops into MIBC in nearly 30% of NMIBC (4,5). Treatment outcomes for MIBC are less favorable, with shorter recurrence-free survival (RFS) and overall survival (OS) (6,7). Early identification of BLCA is closely linked to prognosis. However, patients with early BLCA often do not present with specific symptoms. Therefore, exploring the molecules associated with BLCA is of great importance to monitoring the incidence of BLCA and improving the clinical treatment strategy.

Interleukin 1 receptor-like 2 (IL1RL2), also known as IL36R, is part of the interleukin-1 receptor family. Alongside four other family members interleukin-1 receptor type I, interleukin-1 receptor type II, interleukin-1 receptor-like 1 and interleukin-18 receptor 1-IL1RL2 forms a cluster of cell receptor genes. Research on IL36R primarily focuses on its crucial role as a mediator of inflammatory responses. The three receptor agonists, IL-36 α , IL-36 β and IL-36 γ , bind to the IL-36R complex and exert pleiotropic effects, particularly in the context of inflammatory bowel diseases (8-11). The established interaction between inflammation and cancer recognizes chronic inflammation as a hallmark of cancer (12). High expression of IL1RL2 has been observed in colorectal cancer, demonstrating a pro-metastatic effect and association with patient prognosis (13). IL1RL2 has also been revealed to play a regulatory role in breast, gastric and lung cancer (14-16). However, the relationship between IL1RL2 and BLCA is less understood. Thus, the objective of the present study was to assess the prognostic significance of IL1RL2 in BLCA and investigate its correlation with clinical pathological features of the disease.

Correspondence to: Professor Lihua Sun or Professor Wenzhi Gao, Department of Pathology, Peking University First Hospital-Miyun Hospital, 383 Sunshine Street, Miyun, Beijing 100034, P.R. China
E-mail: chisu0325@sina.cn
E-mail: 1589259358@qq.com

*Contributed equally

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Materials and methods

Clinical specimens. A total of eight pairs of BLCA tissues and adjacent non-cancerous tissues from Peking University First

Hospital-Miyun Hospital were collected between January 2018 and January 2023 (Beijing, China). Each pair of bladder tissue and adjacent non-cancerous tissue came from the same patient. Additionally, 17 pairs of BLCA and adjacent non-cancerous tissues, along with 112 paraffin-embedded BLCA tissue blocks at various stages, were gathered. Data from 112 patients with bladder cancer were incorporated into the Miyun cohort. All patients were pathologically diagnosed with urothelial carcinoma, and the histological characteristics of the samples were confirmed by experienced urological pathologists using hematoxylin-eosin staining. The present study was approved (approval no. 2023-029-001) by the Medical Ethics Committee of Peking University First Hospital-Miyun Hospital (Beijing, China). Clinicopathological characteristics of patients (including sex and age distribution) are listed in Table I.

In silico analysis of IL1RL2 using online datasets. Transcriptome and clinical data from the The Cancer Genome Atlas (TCGA)-BLCA datasets, encompassing 410 patients with bladder carcinoma, were downloaded from UCSC XENA (<https://xena.ucsc.edu/>) (17). The Xiantao tool (<https://www.xiantao.love/>) was used for visualization and analysis of expression differences, prognosis and enrichment (18).

Cell culture. Human ureteral epithelial cells (SV-HUC-1) and human BLCA cell lines (T24, J82, UMUC3 and SW780) were obtained from the American Type Culture Collection and cultured according to the manufacturer's protocols. SV-HUC-1 cells were maintained in F-12K medium (Gibco; Thermo Fisher Scientific, Inc.), while T24, J82, UMUC3 and SW780 cells were cultured in RPMI-1640 medium (Gibco; Thermo Fisher Scientific, Inc.). All media were supplemented with 10% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc.) and 1% penicillin G-streptomycin (Sigma-Aldrich; Merck KGaA). Cultures were kept at 37°C with 5% CO₂.

Reverse transcription-quantitative (RT-q) PCR. RNA was extracted from cells using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.). cDNA synthesis was performed using a reverse transcription system (Tiangen Biotech Co., Ltd.) following the manufacturer's protocol (42°C for 15 min, 95°C for 3 min, 4°C maintenance). RT-qPCR was conducted on the 7500 Reverse transcription PCR System (Applied Biosystems; Thermo Fisher Scientific, Inc.), with GAPDH as the internal reference. The thermocycling conditions were as follows: pre-denaturation at 95°C for 3 min, denaturation at 95°C for 30 sec, annealing extension at 60°C for 30 sec, deformation and annealing extension for 40 cycles. The dissolution curve was increased by 0.5°C every 2 cycles to 95°C. The primer sequences were as follows: IL1RL2 forward, 5'-TCCCGAAGA GTTGTGTTTTGG-3, and reverse, 5'-TGAGTGTGTCAGTAT GGCTTGA-3'; and GAPDH forward, 5'-GGAGCGAGATCC CTCCAAAT-3, and reverse, 5'-GGCTGTTGTCATACT TCTCATGG-3'. The 2^{-ΔΔC_q} method was used for quantification (19).

Western blotting. The primary antibody was incubated at 4°C overnight, and the secondary antibody was incubated at room temperature for 1 h. Total protein was extracted using NP-40 lysis buffer (Beyotime Institute of Biotechnology)

and quantified by the BCA method (Pierce; Thermo Fisher Scientific, Inc.). Proteins were separated by SDS-PAGE (10% gel concentration) and transferred to PVDF membranes. After blocking with 5% skimmed milk for 1 h at room temperature, membranes were incubated with IL1RL2/IL36R antibody (1:1,000; cat. no. 10090; ABclonal Biotech Co., Ltd.) followed by a horseradish peroxidase-conjugated anti-rabbit secondary antibody (1:2,000; cat. no. sc-2004/sc-2005; Santa Cruz Biotechnology, Inc.). GAPDH (1:1,000; cat. no. sc-47724; Santa Cruz Biotechnology, Inc.) served as the internal reference. Immunoreactive bands were visualized using the ECL Plus kit (Applygen Technologies Inc.).

Immunohistochemistry (IHC). Paraffin samples were sliced to a thickness of 5 μm. All paraffin samples were cut by the same pathologist and were of similar thickness. IHC staining was performed using the PV-6000 universal kit (cat. no. IB000088; ZSGB-BIO; OriGene Technologies, Inc.). Sections were heated at 70°C for 1 h, deparaffinized in xylene and rehydrated (95% anhydrous ethanol), followed by antigen retrieval with citrate repair solution at 110°C for 10 min. Slides were incubated at room temperature for 20 min away from light) with endogenous peroxidase inhibitor blocking agent and sheep serum (cat. no. ZU-9022). IL1RL2/IL36R antibody (1:500; cat. no. 10090; ABclonal Biotech Co., Ltd.) was applied (incubated overnight at 4°C in the dark), followed by incubation with a biotinylated secondary antibody (cat. no. 32020; Thermo Fisher Scientific, Inc.; room temperature for 20 min away from light) and staining with the DAB substrate kit (cat. no. ZU-9019; ZSGB-BIO; OriGene Technologies, Inc.). When the background of the slide was brown, reaction was terminated in tap water. Blue was reversed in running tap water for 30 min. Then gradient dehydration with ethanol and xylene was carried out. Finally, it was sealed with neutral resin. IL1RL2 expression was graded based on staining intensity (1, no staining; 2, weak; 3, moderate; 4, strong) and the percentage of reactive cells (1, 0-25%; 2, 26-50%; 3, 51-75%; 4, >75%). The final score (range 1-16) was the product of these variables. The degree of dyeing has several intermediate stages, and the pink brown is also one of them, representing the degree of dyeing. Images were observed using a light microscope.

Statistical analysis. Data were analyzed using GraphPad Prism 9.0 (Dotmatics) or SPSS 20.0 (IBM). Results are expressed as the mean ± SD. Continuous variables were compared using paired and unpaired Student's t-test or one-way ANOVA followed by Bonferroni's post hoc test (for multiple-group comparison) single factor analysis. Pearson's chi-square test or Fisher's exact test were used for correlation analysis. Survival rates were analyzed using the Kaplan-Meier method and log-rank P-tests. Prognostic correlations between clinicopathological and IHC data were assessed by univariate and multivariate Cox regression analyses. *P<0.05 was considered to indicate a statistically significant difference.

Results

IL1RL2 is upregulated in BLCA and associated with tumor stage. To investigate the expression of IL1RL2 in BLCA, IL1RL2 mRNA expression was examined using data from

Table I. Clinicopathologic analysis of IL1RL2 expression in bladder cancer.

Variables	Expression level of IL1RL2 (%)		P-value
	Low	High	
Age, n (%)			0.287
<65	25 (34.7%)	10 (25.0%)	
≥66	47 (65.3%)	30 (75.0%)	
Sex, n (%)			0.091
Male	63 (87.5%)	30 (75.0%)	0.392
Female	9 (12.5%)	10 (25.0%)	
Body mass index	24.83±2.72	24.31±3.60	
Smoking, n (%)			0.700
Yes	22 (31.0%)	11 (27.5%)	
No	49 (69.0%)	29 (72.5%)	
Hypertension, n (%)			0.527
Yes	31 (43.7%)	15 (37.5%)	
No	40 (56.3%)	25 (62.5%)	
Diabetes, n (%)			0.493
Yes	6 (8.4%)	5 (12.5%)	<0.001
No	65 (91.6%)	35 (87.5%)	
Tumor diameter, cm	2.95±2.26	4.79±3.35	
Tumor number, n (%)			0.858
≥3	48 (66.7%)	26 (65.0%)	
<3	24 (33.3%)	14 (35.0%)	
Pathological T, n (%)			<0.001
≤ pT2	69 (95.8%)	20 (50.0%)	
≥ pT3	3 (4.2%)	20 (50.0%)	
Histological grade, n (%)			0.006
G1-2	31 (43.1%)	7 (17.5%)	
G3-4	41 (56.9%)	33 (82.5%)	
Pathological N, n (%)			<0.001
Yes	0 (0.0%)	8 (20.0%)	
No	72 (100.0%)	32 (80.0%)	
State of survival, n (%)			<0.001
Death	7 (9.72%)	15 (37.5%)	
Survival	65 (90.3%)	25 (62.5%)	
Survival time, days	674.11± 315.92	617.91± 371.54	0.408
State of recurrent, n (%)			0.739
Recurrent	16 (22.2%)	10 (25.0%)	
Recurrence-free	56 (77.8%)	30 (75.0%)	
Recurrence-free survival time, days	601.44± 347.13	701.24± 560.84	0.212

the TCGA database. As illustrated in Fig. 1A, IL1RL2 expression in BLCA tissues from TCGA was significantly elevated compared with normal tissues. Data from TCGA indicated upregulated expression of IL1RL2 mRNA in high-stage and high-grade BLCA tissues (Fig. 1B and C). Additionally,

IL1RL2 mRNA was also highly expressed in patients with BLCA and lymph node metastasis (Fig. 1D).

IL1RL2 demonstrates elevated expression in both BLCA cell lines and tissues. RT-qPCR was employed to assess IL1RL2 mRNA levels specifically in BLCA cell lines. The results revealed higher IL1RL2 mRNA expression in the tumor cell lines compared with SV-HUC-1 cells, as depicted in Fig. 2A. Meanwhile, the mRNA expression level of IL1RL2 in BLCA tissues was higher than that in adjacent normal tissues (Fig. 2C). Furthermore, western blot analysis demonstrated an upregulation of IL1RL2 protein expression in both BLCA cell lines (Fig. 2B) and tissues (Fig. 2D). To further understand the IL1RL2 presence in BLCA tissues, IHC was performed on 17 pairs of BLCA tissues and adjacent normal tissues. The results revealed that IL1RL2 was highly expressed in BLCA tissues compared with adjacent normal tissues (Fig. 2E and F).

IL1RL2 is highly expressed in high-stage and high-grade BLCA. IHC scoring based on different staining intensities (Fig. 3A) and areas was performed. The average IHC score of IL1RL2 expression in patients with high-stage and high-grade BLCA was significantly higher than in low-stage (P<0.001; Fig. 3B) and low-grade BLCA (P<0.01; Fig. 3C; Table I). Patients with BLCA with lymph node metastasis demonstrated a significantly higher average IHC score of IL1RL2 expression compared with non-metastatic patients (P<0.001; Fig. 3D).

High IL1RL2 expression is associated with improved OS in patients with BLCA. To evaluate the diagnostic potential of IL1RL2, the differential expression in BLCA vs. adjacent normal tissues was analyzed, generating receiver operator characteristic (ROC) curves using data from the TCGA database and a cohort of 112 patients with BLCA. The ROC curves revealed that IL1RL2 expression distinguished tumors from adjacent normal tissues with an AUC of 0.700 (95% CI: 0.579-0.821) in TCGA and 0.647 (95% CI: 0.497-0.797) in Miyun chart database (Fig. 4A and B). IHC analysis of 112 patients with BLCA at different stages and grades revealed a correlation between OS time and IL1RL2 expression (Fig. 4C). For OS analysis, in univariate analysis, IL1RL2 expression was negatively correlated with OS (95% CI: 0.072-0.552; P=0.002); and smoking (95% CI: 1.091-22.834; P=0.038), age (95% CI: 1.035-1.175; P=0.003) and lymph node metastasis (95% CI: 0.024-0.502; P=0.004) were also factors influencing OS (Table II). In multivariate analysis, smoking (95% CI: 1.024-28.661; P=0.047), age (95% CI: 1.028-1.190; P=0.007) and IL1RL2 expression (95% CI: 0.089-0.988; P=0.048) were associated with poorer OS. A line chart predicting survival was constructed based on smoking, age and IL1RL2 (Fig. 4D). For RFS analysis, in univariate analysis, sex (95% CI: 0.116-0.939; P=0.038) and pathological stage (95% CI: 0.136-0.989; P=0.047) were factors influencing RFS, while IL1RL2 was not a factor for RFS (Table SI). In multivariate analysis, sex (95% CI: 0.332 (0.116-0.949; P=0.0039) was associated with poorer RFS, suggesting that sex may be an independent prognostic factor for patients with BLCA. In TCGA database, High levels of IL1RL2 expression were associated with lower disease-specific survival and progression-free survival (Fig. 4E and F).

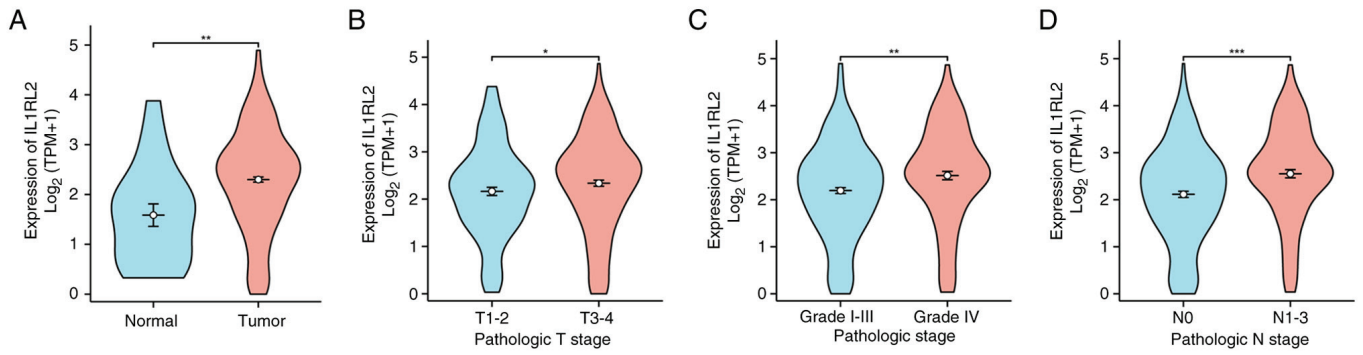


Figure 1. mRNA expression of IL1RL2 in BLCA. (A) The mRNA expression of IL1RL2 in TCGA clinical samples. (B-D) The expression of IL1RL2 in patients with BLCA with different (B) pathological T stages, (C) grades and (D) lymphatic metastases. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ (using unpaired Student's t-test). IL1RL2, interleukin-1 receptor-like 2; BLCA, bladder cancer; TCGA, The Cancer Genome Atlas.

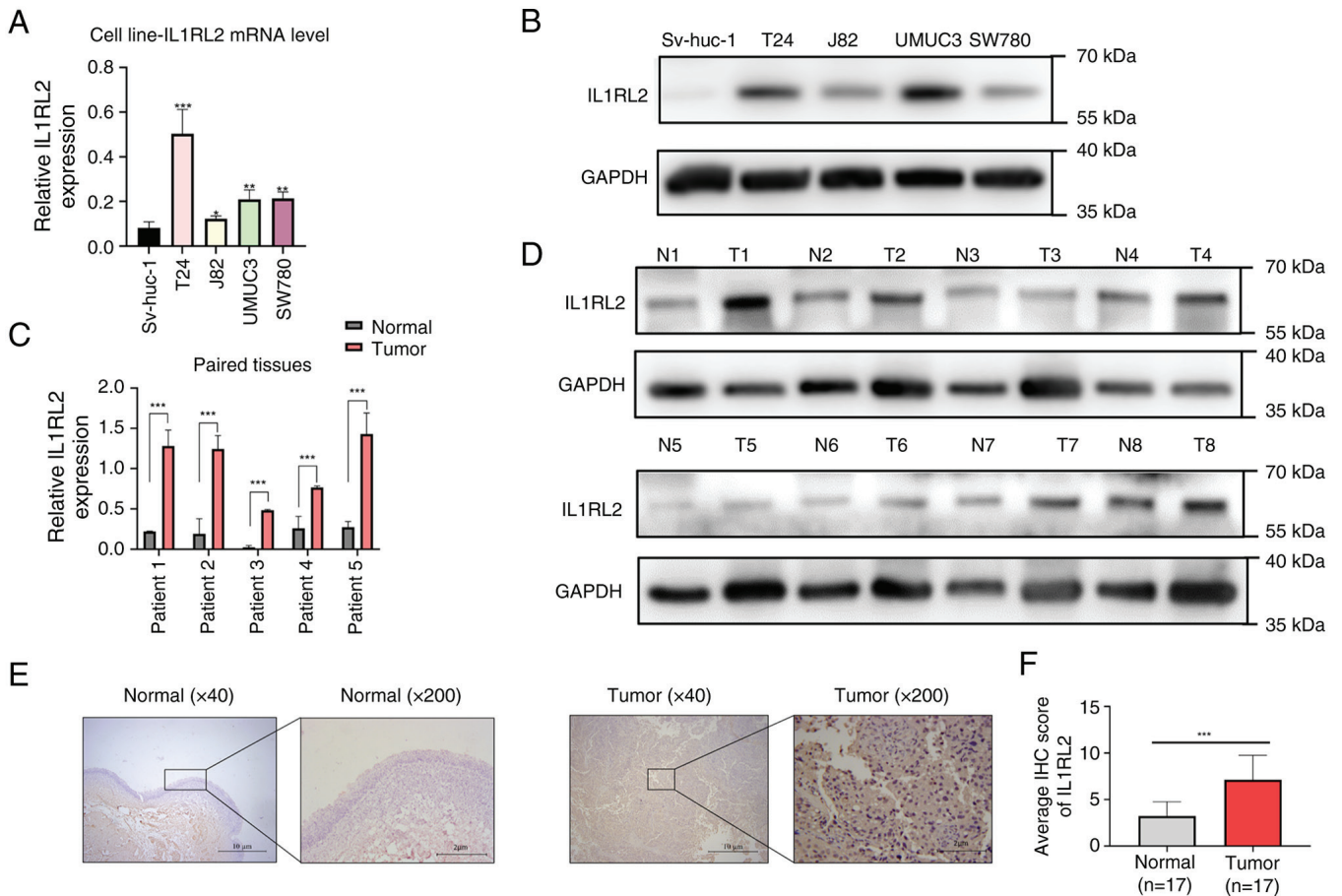


Figure 2. IL1RL2 is highly expressed in BLCA cell lines and tissues. (A) IL1RL2 mRNA expression in BLCA cell lines compared with normal uroepithelial SV-HUC-1 cells [one-way ANOVA followed by Bonferroni's post hoc test (for multiple-group comparison) single factor analysis]. (B) IL1RL2 protein expression in BLCA cell lines. (C) IL1RL2 mRNA expression in five paired BLCA tissues and adjacent normal mucosa (using paired Student's t-test). (D) IL1RL2 protein expression in eight paired BLCA tissues. (E) IHC of BLCA tissues and adjacent normal tissues. The left image represents the normal mucosa and the right image represents the BLCA tissue (using unpaired Student's t-test). (F) The histogram represents the average IHC score of IL1RL2. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. IL1RL2, interleukin-1 receptor-like 2; BLCA, bladder cancer; N, normal; T, tumor; IHC, immunohistochemistry.

To explore the functional implications of IL1RL2 in BLCA, enrichment analysis of Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were performed using genes co-expressed with IL1RL2 obtained from the TCGA BLCA database. This analysis aimed to uncover the biological roles associated with IL1RL2 in BLCA. In GO enrichment analysis, cell-cell

junction, epidermis development and MAP kinase activity were enriched (Fig. 5A). KEGG enrichment highlighted MAPK signaling pathway and *Salmonella* infection (Fig. 5A). Additionally, Gene Set Enrichment Analysis (GSEA) in BLCA indicated that elevated IL1RL2 expression was linked to several critical processes that promote tumorigenesis, including tumor immune infiltration-related processes such

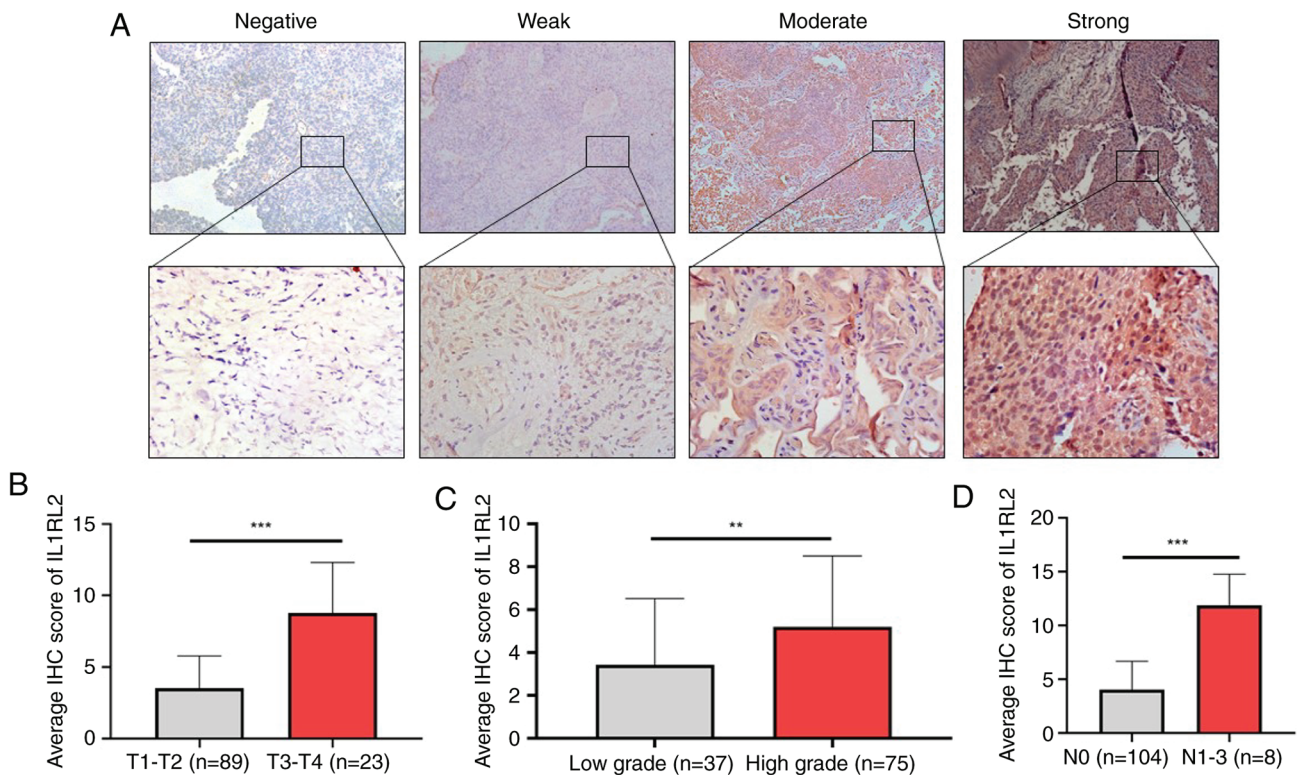


Figure 3. IL1RL2 is highly expressed in BLCA with high stage, high grade and lymphatic metastasis. (A) The difference is made according to the degree of IHC staining. (B-D) IL1RL2 was measured in different (B) pathological stages, (C) grades and (D) lymphatic metastatic mean IHC scores of BLCA (using unpaired Student's t-test). ** $P < 0.01$ and *** $P < 0.001$. IL1RL2, interleukin-1 receptor-like 2; BLCA, bladder cancer; IHC, immunohistochemistry.

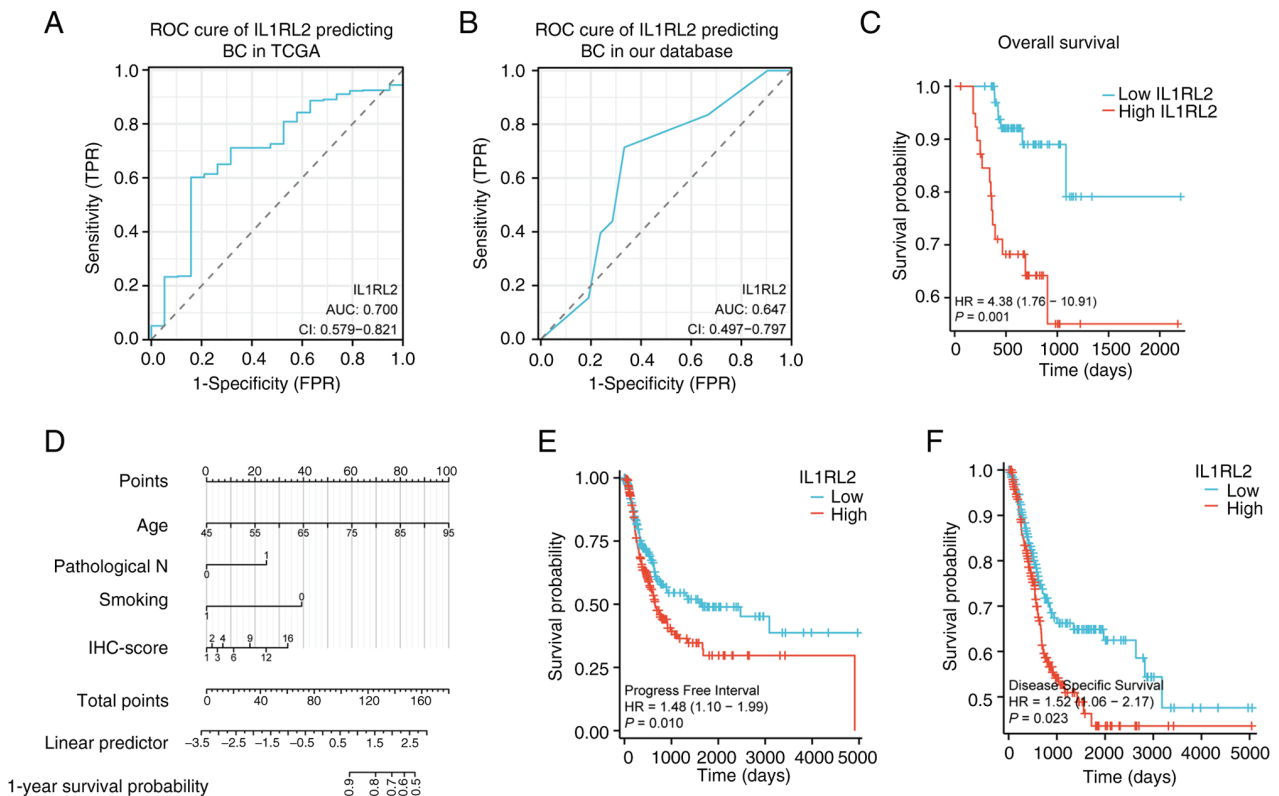


Figure 4. High IL1RL2 expression is associated with poor survival in patients with BLCA. (A and B) ROC curve of IL1RL2 expression to predict patients with BLCA in (A) TCGA database and (B) Miyun chart database. (C) Kaplan-Meier survival curves for the overall survival of patients with BLCA based on IL1RL2 expression in our database. (D) Nomogram to predict the 1-year overall survival of patients with BLCA. (E and F) Kaplan-Meier survival curves for the disease-specific survival and progression-free survival of patients with BLCA based on IL1RL2 expression in TCGA. IL1RL2, interleukin-1 receptor-like 2; BLCA, bladder cancer; ROC, receiver operator characteristic; TCGA, The Cancer Genome Atlas; AUC, area under curve; CI, confidence interval; HR, hazard ratio.

Table II. Univariate analysis and multivariate analysis of overall survival of bladder cancer in Miyun chart database.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
IL1RL2 level, high vs. low	0.200 (0.072-0.552)	0.002	0.296 (0.089-0.988)	0.048
Smoking, yes vs. no	4.994 (1.091-22.834)	0.038	5.417 (1.024-28.661)	0.047
Hypertension, yes vs. no	2.000 (0.711-5.625)	0.189		
Diabetes, yes vs. no	0.585 (0.141-2.426)	0.46		
Tumor diameter	0.981 (0.826-1.166)	0.83		
Tumor number, ≥3 vs. <3	1.603 (0.608-4.231)	0.34		
Body mass index	0.920 (0.787-1.076)	0.298		
Age	1.103 (1.035-1.175)	0.003	1.106 (1.028-1.190)	0.007
Sex, male vs. female	0.839 (0.247-2.847)	0.778		
Pathological T, T3 + T4 vs. T1 + T2	0.789 (0.225-2.440)	0.681		
Pathological N, N1-3 vs. N0	0.109 (0.024-0.502)	0.004	0.210 (0.035-1.258)	0.088
Histological grade, high vs. low	1.033 (0.378-2.824)	0.949		

HR, hazard ratio; CI, confidence interval.

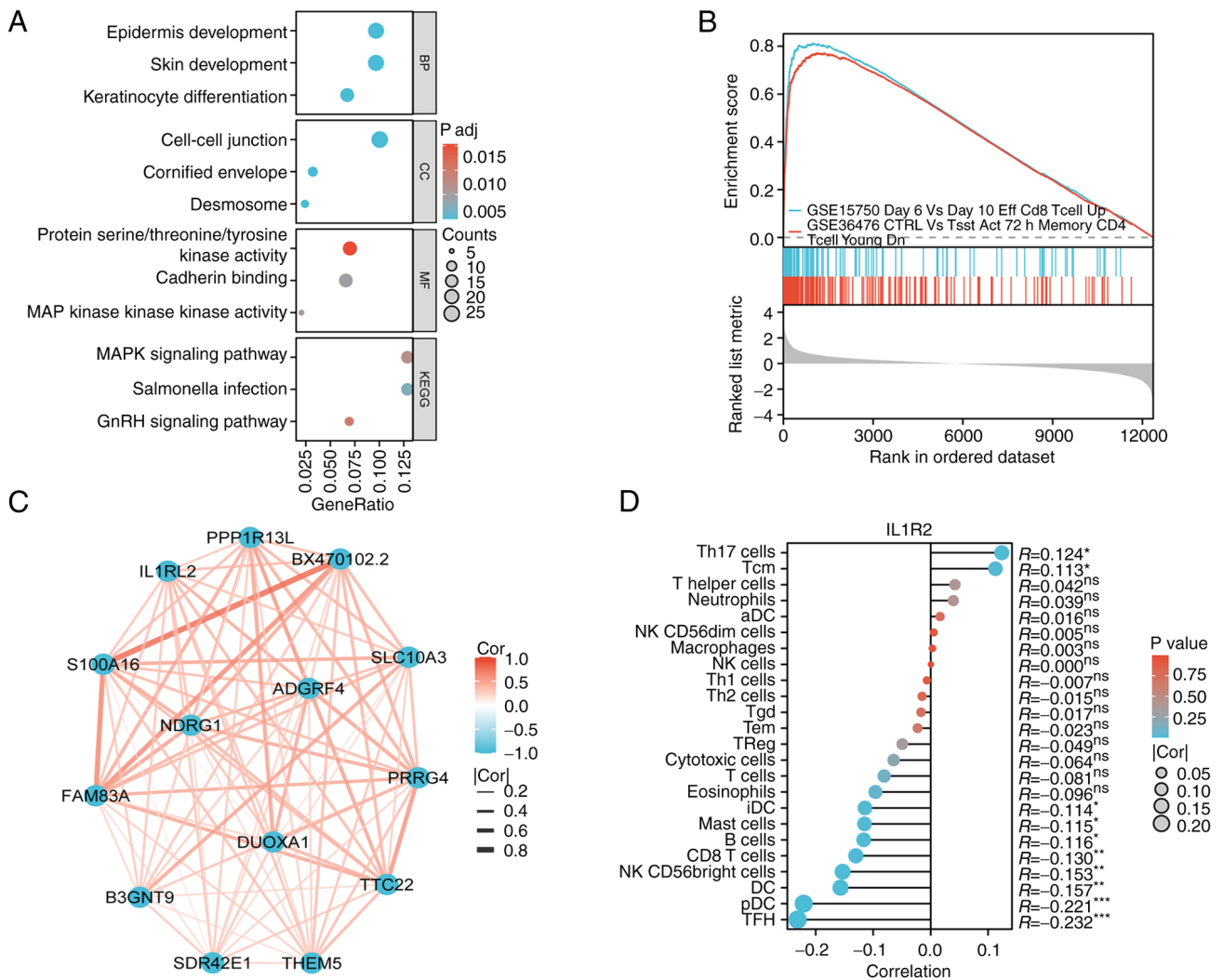


Figure 5. Functional prediction of IL1RL2 in BLCA by enrichment analysis. (A) Gene Ontology term and KEGG pathway enrichment analysis results for genes co-expressed with IL1RL2 in BLCA. (B) Gene Set Enrichment Analysis was performed in The Cancer Genome Atlas database according to the expression level of IL1RL2. (C) The protein-protein interaction network of IL1RL2 and its potential targets. (D) Immuno-infiltration correlation analysis of IL1RL2. IL1RL2, interleukin-1 receptor-like 2; BLCA, bladder cancer; KEGG, Kyoto Encyclopedia of Genes and Genomes.

as CD8 T cells and memory CD4 (Fig. 5B), suggesting that IL1RL2 may facilitate bladder tumor development. Protein-protein interaction analysis revealed that potential targets of IL1RL2 were primarily genes associated with cell proliferation and migration (Fig. 5C). Immuno-infiltration analysis of IL1RL2 in BLCA revealed potential associations with plasmacytoid dendritic cells (pDC) and T follicular helper cells (TFH) (Fig. 5D). Overall, these results suggested that IL1RL2 may regulate tumor development through modulation of the tumor immune microenvironment and MAPK signaling pathway.

Discussion

BLCA is a common malignancy with a high recurrence rate and potential for metastasis (20). Despite continuous advancements in medical care over the past decades, there has been limited improvement in the treatment outcomes and diagnostic methods for BLCA (21). Identifying specific genes expressed at the molecular level in BLCA could contribute to its diagnosis and treatment. Currently, there is no reported research on the role of IL1RL2 in BLCA. The present study revealed that IL1RL2 is upregulated in BLCA and correlated with the stage, grade, lymph node album and prognosis of BLCA.

Early diagnosis and monitoring of BLCA are crucial for improving patient prognosis. Numerous diagnostic biomarkers have been identified in previous studies. Lokeshwar *et al* (22) found that BTA testing has high sensitivity and specificity in patients with BLCA. Additionally, Grossman *et al* (23) demonstrated that NMP22 testing can effectively distinguish patients with BLCA from healthy individuals. However, current diagnostic methods are still limited, and there is a need to improve both sensitivity and specificity.

IL1RL2 has been identified as a novel diagnostic and prognostic marker in various cancer types, such as breast, gastric, colorectal and lung cancer, suggesting its potential as both a diagnostic marker and therapeutic target (19,24-27). Baker *et al* (27) found that IL1RL2 agonists promote the progression of human and murine lung cancer, leading to tumor cell proliferation and migration. The team also discovered high expression of IL1RL2 in colorectal cancer, with a concurrent role in promoting colorectal cancer metastasis (13). These results suggested that IL1RL2 plays a crucial role in tumorigenesis and development.

In the present study, through analysis of TCGA and 112 samples of patients with BLCA database, the abundance of IL1RL2 in BLCA and its clinical significance were explored and confirmed. The results indicated that IL1RL2 is upregulated in both BLCA tissues and cells. The IL1RL2 level is significantly correlated with tumor stage, grade and metastasis. Furthermore, IHC analysis revealed that IL1RL2 expression is an independent risk factor for OS. Additionally, Kaplan-Meier survival analysis using TCGA and 112 patients with BLCA from Miyun chart database revealed that upregulated IL1RL2 status is associated with lower disease-specific survival and progression-free interval rates. These data suggested that IL1RL2 is associated with BLCA survival and tumor progression.

To further analyze the oncogenic role of IL1RL2 in BLCA, a bioinformatics analysis was performed for

functional prediction. Enrichment analysis suggested that IL1RL2 may participate in the MAPK signaling pathway, a pathway crucial for tumor proliferation, migration and invasion (28-30). GSEA enrichment revealed the enrichment of immune cells, such as CD4 and CD8, indicating that IL1RL2 may regulate tumor progression through modulation of the tumor immune microenvironment. Immuno-infiltration analysis of IL1RL2 in BLCA suggested potential associations with pDC and TFH.

While the present study has identified the expression profile of IL1RL2 in BLCA, the oncogenic functions of IL1RL2 in BLCA need further clarification both *in vitro* and *in vivo*. Additionally, the specific molecular mechanisms through which IL1RL2 operates require further exploration. IL1RL2 has the potential to serve as a molecular marker for the assessment of BLCA prognosis and help clinicians develop more individualized treatment strategies. The present study provided new ideas and potential molecular targets for the early diagnosis, prognosis assessment and individualized treatment of BLCA.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XH, YL, LS and WG conceptualized and designed the present study. LS and WG provided administrative support. XH, YL, ZG, JC, YN, LS, WG provided the study materials or recruited patients. WG collected and assembled the data. XH and YL analyzed and interpreted the data. XH and YL confirm the authenticity of all the raw data. All authors contributed to manuscript writing, and read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved (approval no. 2023-029-001) by the Ethics Committee of Peking University First Hospital-Miyun Hospital (Beijing, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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