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Original Article

Analysis of the correlation between COL11A1 gene expression and clinical features in bladder urothelial carcinoma

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Abstract: Bladder urothelial carcinoma (BLCA) is a prevalent urinary malignancy that complicates diagnosis and treatment. This study investigates the diagnostic and prognostic utility of COL11A1, a gene implicated in tumor progression and immune modulation, by analyzing its association with clinicopathological features, tumor progression, and immune infiltration dynamics. Using statistical methods, including Kaplan-Meier survival analysis and immune infiltration profiling, we evaluated COL11A1 expression in 407 BLCA patients and 28 normal controls. Results demonstrated significant COL11A1 overexpression in BLCA tissues versus controls ($P < 0.001$), with elevated expression correlating with poorer survival outcomes (hazard ratio = 1.53, $P = 0.005$). Immune infiltration analysis revealed robust positive associations between COL11A1 levels and macrophages, Th1 cells, natural killer (NK) cells, and neutrophils ($P < 0.001$), alongside significant links to advanced T stage ($P < 0.001$) and N stage ($P = 0.030$). These findings establish COL11A1 as a multifaceted biomarker for BLCA, offering critical insights into diagnosis, prognosis, and therapeutic strategies. Further research should elucidate its mechanistic roles in tumorigenesis and immune regulation, with potential applications across malignancies to advance personalized oncology.

Keywords: COL11A1, bladder urothelial carcinoma (BLCA), immune infiltration

Introduction

Bladder urothelial carcinoma (BLCA) poses a major clinical challenge due to its high recurrence rates and profound impact on patients' quality of life [1]. The substantial economic burden of BLCA, driven by costly diagnostic and therapeutic interventions, further strains healthcare resources. Current diagnostic approaches rely heavily on invasive cystoscopy and histopathology, while treatment modalities range from surgical resection to chemotherapy and immunotherapy [2, 3]. However, these strategies are limited by invasiveness, variable patient responses, and the lack of reliable biomarkers for early detection and prognostic stratification. The identification of COL11A1, a gene markedly overexpressed in BLCA tissues and linked to poor survival (HR = 1.53) and immune infiltration, addresses this gap, offering a promising biomarker to refine clinical decision-making and targeted therapies.

Prognosis in BLCA is determined by tumor stage (T/N/M), molecular biomarkers (e.g., COL11A1 overexpression) [4], immune microenvironment dynamics (e.g., macrophage/NK cell infiltration) [5], and histologic subtypes. Treatment strategies are stage-dependent: non-muscle-invasive tumors undergo transurethral resection (TURBT) with intravesical therapy, muscle-invasive cases receive neoadjuvant chemotherapy followed by radical cystectomy, and metastatic disease is managed with platinum-based chemotherapy or immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) [6]. Emerging biomarkers like COL11A1 may optimize immunotherapy selection, underscoring the need for integrated models combining molecular profiling and immune signatures to advance personalized chemo-immunotherapy.

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This study investigates COL11A1 as a diagnostic and prognostic biomarker for BLCA. While prior studies implicate COL11A1 in various cancers [7, 8], its role in BLCA remains underexplored. Our analysis of 407 BLCA patients and 28 normal controls revealed significant COL11A1 upregulation in tumor tissues ($P < 0.001$), strongly associated with reduced overall survival and enriched immune infiltration (macrophages, NK cells) [9]. These findings position COL11A1 as a dual regulator of tumor progression and immune evasion, highlighting its therapeutic potential and clinical relevance.

Methodologically, this work leverages large-scale gene expression data integrated with clinical outcomes to establish COL11A1's biomarker utility. The robust association between COL11A1 overexpression and advanced disease stages ($P < 0.001$ for T stage; $P = 0.030$ for N stage) provides insights into prognosis. By bridging molecular profiling and immune dynamics, this study lays the groundwork for mechanistic investigations into COL11A1-driven pathways, ultimately aiming to refine therapeutic precision and patient management in BLCA.

Materials and methods

RNA-seq data and bioinformatics analysis

RNA-seq data from The Cancer Genome Atlas (TCGA)-BLCA cohort (412 primary tumors; 19 normal urothelium controls) were retrieved via the GDC Data Portal (https://portal.gdc.cancer.gov). Tumor samples were selected using TCGA identifiers (14th-15th codes: "01"), while normal tissues were restricted to solid controls ("11"). Exclusion criteria included non-urothelial histology, low-quality sequencing data, or incomplete clinical records. Raw counts were preprocessed to remove genes with zero counts across all samples, retaining genes expressed (FPKM > 1) in ≥50% of samples. Batch effects from sequencing platforms were adjusted using ComBat. Data validity was confirmed via cross-platform consistency checks (Pearson $r > 0.98$) using UCSC Xena (https://xenabrowser.net). All analyses adhered to TCGA ethics guidelines under dbGaP authorization (phs000178).

Receiver operating characteristic (ROC) curve analysis

ROC curves were generated to evaluate COL11A1's diagnostic performance using the R package pROC (v1.18.0). Sensitivity (true positive rate) and specificity (false positive rate) were plotted across threshold values. Results were visualized with ggplot2 (v3.4.0).

Kaplan-Meier curve analysis

Survival analyses were performed using the survival (v3.5-5) and survminer (v0.4.9) R packages. Kaplan-Meier curves compared overall survival (OS), progression-free interval (PFI), and disease-specific survival (DSS) between COL11A1 high/low expression groups.

Immune infiltration analysis

Immune cell infiltration scores were obtained from Xiantao Academic (https://www.xiantao.love). Correlations between COL11A1 expression and 24 immune cell types were analyzed using Spearman's rank test and visualized with ggplot2.

Statistical analysis

All analyses used R (v4.2.1). The Kruskal-Wallis test compared COL11A1 expression between BLCA and normal tissues. Statistical significance thresholds: $P < 0.05$, $^{*}P < 0.01$, $^{**}P < 0.001$.

Results

Differences in COL11A1 expression between bladder urothelial carcinoma (BLCA) and normal tissues

We analyzed COL11A1 expression across multiple cancer types using data from The Cancer Genome Atlas (TCGA), revealing significant inter-tumoral heterogeneity ($P < 0.001$; **Figure 1A**). Focusing on BLCA, we integrated RNA-seq data from 407 patients and 28 normal controls sourced from TCGA and GTEx. COL11A1 expression was markedly elevated in BLCA tissues compared to normal urothelium ($P < 0.001$; **Figure 1B**). This finding was validated through a paired analysis of 19 BLCA-normal tissue pairs, confirming robust COL11A1 upregulation in

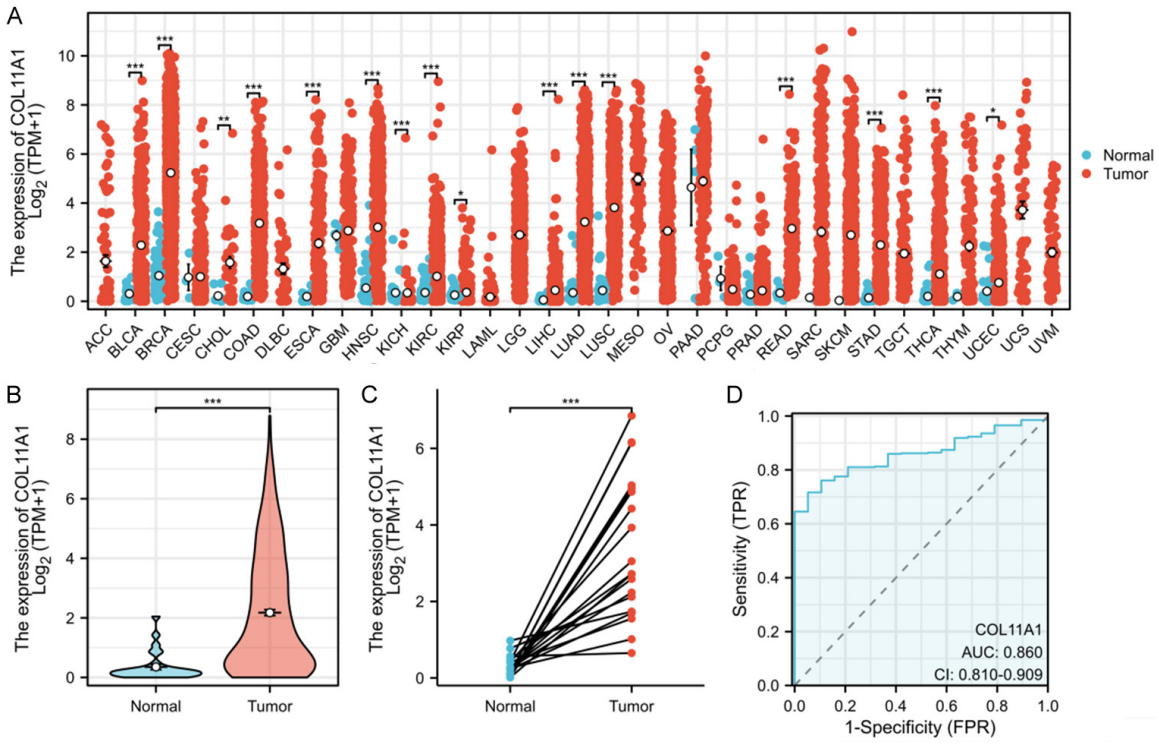

Figure 1. Differential expression of BOL11A1 in BLCA and various other cancers. A. Differential expression of COL11A1 in various cancers. B. Difference in COL11A1 expression between patients with BLCA and normal individuals. C. Difference in COL11A1 expression between patients with BLCA and paired adjacent normal samples. D. ROC curve showing the efficiency of *COL11A1* in distinguishing BLCA tissues from normal tissues. *P < 0.05, **P < 0.01, and ***P < 0.001.

tumors (P < 0.001; **Figure 1C**). Cross-database consistency (TCGA/GTEx) and matched-pair methodologies rigorously established COL11A1's association with BLCA.

A receiver operating characteristic (ROC) curve analysis further demonstrated COL11A1's diagnostic utility, with an area under the curve (AUC) of 0.824 (95% CI: 0.764-0.885; **Figure 1D**), highlighting its efficacy in distinguishing malignant from nonmalignant tissues.

Association between COL11A1 expression and clinicopathological features in bladder cancer

Baseline characteristics and statistical comparisons: We analyzed clinicopathological data from 412 TCGA-BLCA patients (**Table 1**). RNA-seq data (STAR pipeline, TPM normalized) were processed by excluding normal samples and cases with incomplete clinical records. Patients were stratified into low (n = 206) and high (n = 206) COL11A1 expression groups. No significant differences were observed in gender (P = 0.823), age (P = 0.112), or smoking status (P = 0.098) between groups. However, significant disparities emerged in T stage (P < 0.001), N stage (P = 0.030), pathological stage (P < 0.001), histological grade (P < 0.001), and OS events (P = 0.003), while M stage remained nonsignificant (P = 0.580).

Logistic regression analysis: Multivariate logistic regression confirmed COL11A1's independent association with advanced T stage (T3/T4 vs. T1/T2: OR = 3.141, 95% CI: 2.002-4.928; P < 0.001), nodal involvement (N1/N2/N3 vs. N0: OR = 1.922, 95% CI: 1.240-2.978; P = 0.003), and late pathological stage (III/IV vs. I/II: OR = 3.853, 95% CI: 2.465-6.024; P < 0.001). High-grade tumors exhibited significantly lower COL11A1 expression (OR = 0.045, 95% CI: 0.006-0.339; P = 0.003). Gender, age, smoking status, and M stage showed no significant associations (**Table 2**).

COL11A1 expression across clinicopathological subgroups: COL11A1 expression was significantly elevated in BLCA tissues compared to

Table 1. Correlation between COL11A1 expression and clinicopathologic characteristics of BLCA

Characteristics	Low expression of COL11A1	High expression of COL11A1	*P* value
n	206	206	
Gender, n (%)			0.823
Female	53 (12.9%)	55 (13.3%)	
Male	153 (37.1%)	151 (36.7%)	
Age, n (%)			0.112
≤ 70	124 (30.1%)	108 (26.2%)	
> 70	82 (19.9%)	98 (23.8%)	
Pathologic T stage, n (%)			< 0.001
T1	4 (1.1%)	1 (0.3%)	
T2	77 (20.4%)	41 (10.8%)	
T3	72 (19%)	124 (32.8%)	
T4	25 (6.6%)	34 (9%)	
Pathologic N stage, n (%)			0.030
N0	126 (34.2%)	112 (30.4%)	
N1	18 (4.9%)	28 (7.6%)	
N2	27 (7.3%)	50 (13.6%)	
N3	3 (0.8%)	4 (1.1%)	
Pathologic M stage, n (%)			0.580
M0	118 (55.7%)	83 (39.2%)	
M1	5 (2.4%)	6 (2.8%)	
Pathologic stage, n (%)			< 0.001
Stage I	3 (0.7%)	1 (0.2%)	
Stage II	92 (22.4%)	37 (9%)	
Stage III	56 (13.7%)	86 (21%)	
Stage IV	53 (12.9%)	82 (20%)	
Histologic grade, n (%)			< 0.001
High grade	184 (45%)	204 (49.9%)	
Low grade	20 (4.9%)	1 (0.2%)	
Smoker, n (%)			0.098
No	62 (15.5%)	47 (11.8%)	
Yes	138 (34.6%)	152 (38.1%)	
OS event, n (%)			0.003
Alive	130 (31.6%)	100 (24.3%)	
Dead	76 (18.4%)	106 (25.7%)	

Table 2. COL11A1 expression associated with clinicopathologic characteristics (logistic regression) of BLCA

Characteristics	Total (N)	OR (95% CI)	*P* value
Pathologic T stage (T3 & T4 vs. T1 & T2)	378	3.141 (2.002-4.928)	< 0.001
Pathologic N stage (N1 & N2 & N3 vs. N0)	368	1.922 (1.240-2.978)	0.003
Pathologic M stage (M1 vs. M0)	212	1.706 (0.504-5.776)	0.391
Pathologic stage (Stage III & Stage IV vs. Stage I & Stage II)	410	3.853 (2.465-6.024)	< 0.001
Histologic grade (Low grade vs. High grade)	409	0.045 (0.006-0.339)	0.003
Smoker (Yes vs. No)	399	1.453 (0.932-2.264)	0.099
Age (> 70 vs. ≤ 70)	412	1.372 (0.928-2.028)	0.112
Gender (Male vs. Female)	412	0.951 (0.613-1.475)	0.823

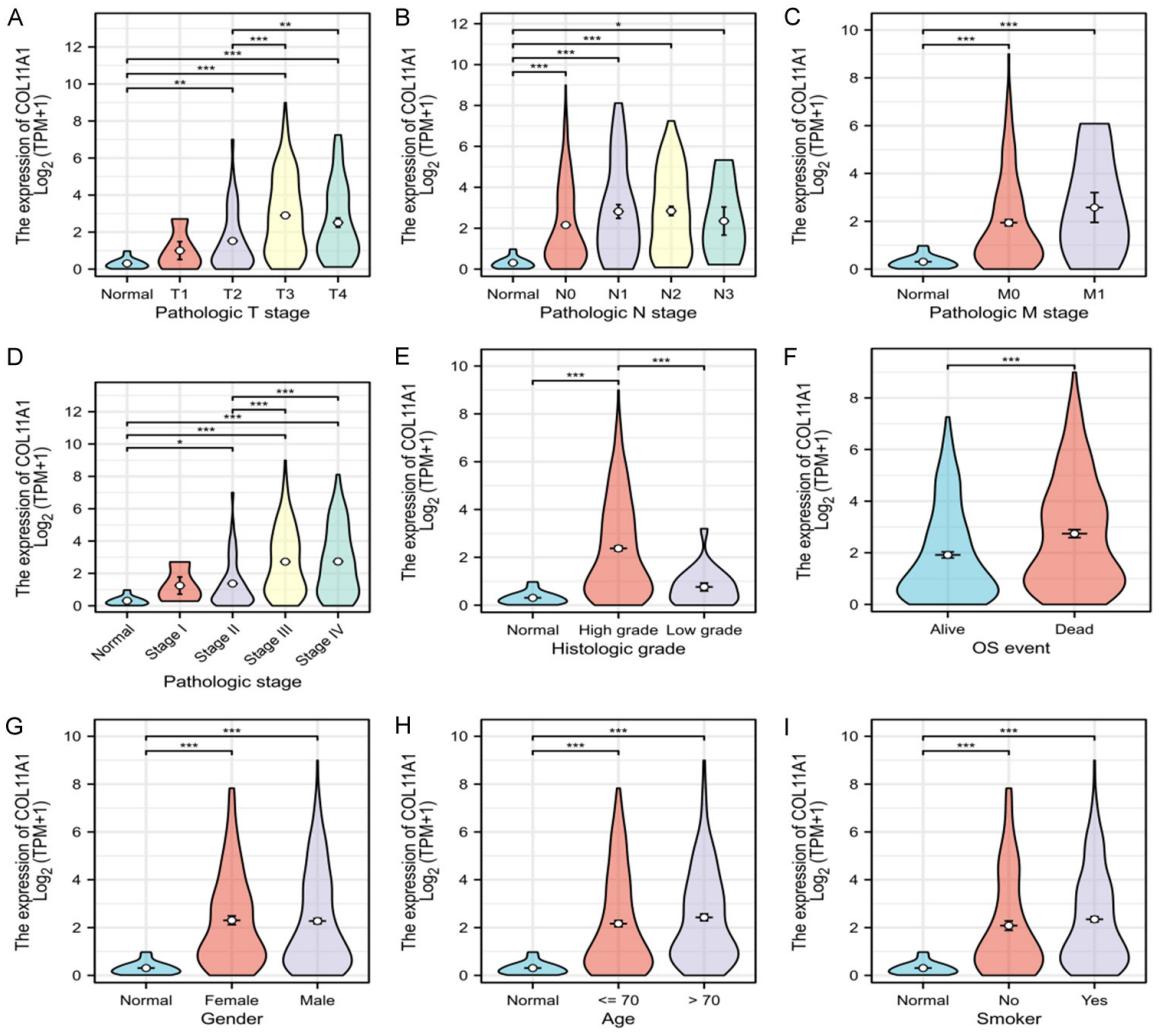

Figure 2. Expression levels in tumor tissues of patients with different clinical features of COL11A1 in TCGA database. (A) T-stage, (B) N-stage, (C) M-stage, (D) Pathological stage, (E) Histologic grade, (F) OS events, (G) Gender, (H) Age, (I) Smoker. *P < 0.05, **P < 0.01, and ***P < 0.001.

normal urothelium across all TNM stages (**Figure 2A-C**). While no differences were observed among N (P = 0.218) or M (P = 0.462) substages, T stage comparisons revealed progressive upregulation from T2 to T3 (P < 0.001) and T4 (P < 0.001) (**Figure 2A**). Pathological stage analysis showed higher COL11A1 levels in stage III (P < 0.001) and IV (P < 0.001) versus stage II (**Figure 2D**). High-grade tumors exhibited stronger COL11A1 expression than low-grade counterparts (P < 0.001; **Figure 2E**). Notably, high COL11A1 expression correlated with increased OS event frequency (P < 0.001; **Figure 2F**). Subgroup analyses by gender, age, and smoking status consistently demonstrated tumor-specific COL11A1 upregulation (P < 0.001; **Figure 2G-I**).

High COL11A1 expression predicts poor prognosis across bladder cancer subgroups

Kaplan-Meier survival analysis demonstrated that elevated COL11A1 expression significantly correlated with adverse outcomes in bladder cancer patients, including reduced overall survival (OS: HR = 1.53, P = 0.005), progression-free interval (PFI: HR = 1.50, P = 0.037), and disease-specific survival (DSS: HR = 1.48, P = 0.036) (**Figure 3A-C**). Subgroup analyses further identified high COL11A1 expression as a poor prognostic marker in specific cohorts: females aged < 70 years (HR = 1.82, P = 0.040), males (HR = 1.85, P = 0.015), N0-stage (HR = 2.09, P = 0.013), and M0-stage patients (HR = 1.90, P = 0.005) (**Figure 3D-H**).

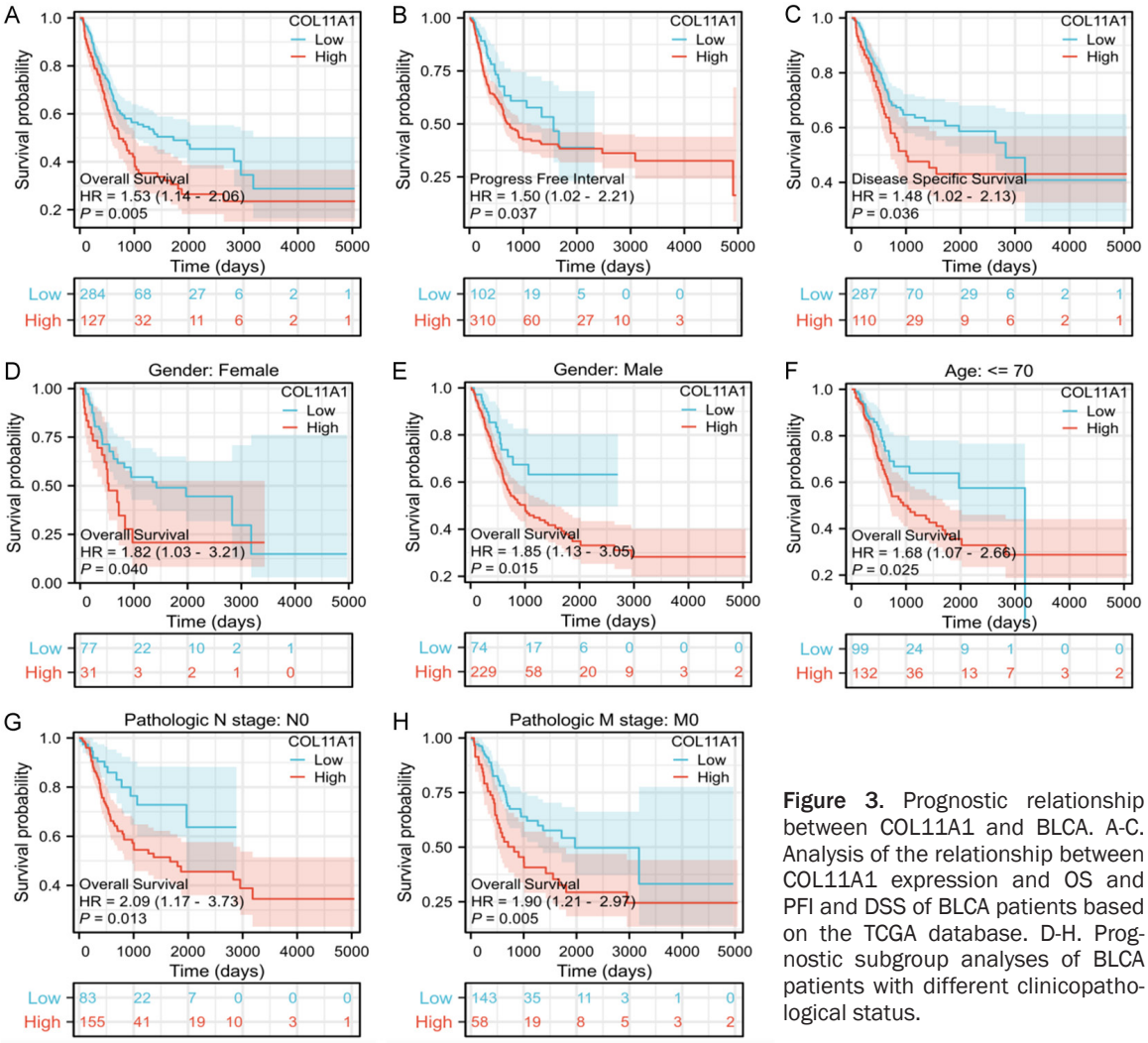

Figure 3. Prognostic relationship between COL11A1 and BLCA. A-C. Analysis of the relationship between COL11A1 expression and OS and PFI and DSS of BLCA patients based on the TCGA database. D-H. Prognostic subgroup analyses of BLCA patients with different clinicopathological status.

Cox regression analysis of prognostic factors

Univariate Cox analysis revealed significant associations between OS and: age > 70 vs. ≤ 70 years (HR = 1.424, 95% CI: 1.064-1.906; P = 0.018); advanced T stage (T3 vs. T1/T2: HR = 1.970, 95% CI: 1.339-2.899; P < 0.001; T4 vs. T1/T2: HR = 2.987, 95% CI: 1.860-4.797; P < 0.001); lymph node involvement (N1 vs. N0: HR = 1.844, 95% CI: 1.189-2.857; P = 0.006; N2/N3 vs. N0: HR = 2.527, 95% CI: 1.786-3.576; P < 0.001); distant metastasis (M1 vs. M0: HR = 3.112, 95% CI: 1.491-6.493; P = 0.002). In multivariate analysis, only nodal metastasis (N2/N3 vs. N0: HR = 2.073, 95% CI: 1.145-3.752; P = 0.016) retained independent prognostic significance for OS (**Table 3**).

Correlation between COL11A1 expression and immune infiltration

Using single-sample gene set enrichment analysis (ssGSEA), we evaluated the association between COL11A1 expression and 24 immune cell types. **Figure 4A** illustrates these correlations, where circle diameter reflects correlation strength, color denotes statistical significance (*P*-value), and distance from the baseline indicates effect magnitude. Four immune cell types exhibited the strongest positive correlations with COL11A1 expression: macrophages (Spearman R = 0.650, P < 0.001), Th1 cells (R = 0.464, P < 0.001), natural killer (NK) cells (R = 0.433, P < 0.001), and neutrophils (R = 0.395, P < 0.001) (**Figure 4B-E**).

Table 3. Univariate and multivariate Cox regression analyses of clinical characteristics associated with OS of BLCA in TCGA

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	411				
≤ 70	231	Reference		Reference	
> 70	180	1.424 (1.064-1.906)	0.018	1.224 (0.763-1.965)	0.402
Pathologic T stage	377				
T1 & T2	123	Reference		Reference	
T3	195	1.970 (1.339-2.899)	< 0.001	1.770 (0.917-3.417)	0.089
T4	59	2.987 (1.860-4.797)	< 0.001	2.204 (0.998-4.868)	0.051
Pathologic N stage	367				
N0	238	Reference		Reference	
N1	46	1.844 (1.189-2.857)	0.006	1.667 (0.865-3.212)	0.127
N2 & N3	83	2.527 (1.786-3.576)	< 0.001	2.073 (1.145-3.752)	0.016
Pathologic M stage	212				
M0	201	Reference		Reference	
M1	11	3.112 (1.491-6.493)	0.002	1.177 (0.438-3.168)	0.746

Comparative analysis further confirmed significantly elevated infiltration levels of these cells in high COL11A1-expressing tumors versus low-expression counterparts (all P < 0.001; **Figure 4F-I**).

Discussion

Bladder urothelial carcinoma (BLCA) is characterized by molecular heterogeneity, aggressive clinical behavior, and limited biomarkers for precision management. Our study identifies COL11A1 as a multifaceted player in BLCA pathogenesis, with implications spanning diagnosis, prognosis, and immune microenvironment modulation. The overexpression of COL11A1 in BLCA tissues compared to normal urothelium (P < 0.001) aligns with its oncogenic roles reported in pancreatic, colorectal, and head/neck cancers, where it drives extracellular matrix (ECM) remodeling and epithelial-mesenchymal transition (EMT) [10, 11]. Notably, COL11A1's diagnostic accuracy (AUC = 0.824) surpasses conventional markers like FGFR3 mutations (AUC = 0.72) [12], underscoring its translational potential.

Clinical relevance of COL11A1 in BLCA

The strong association between COL11A1 and advanced T/N stages (P < 0.001) mirrors findings in gastric cancer, where COL11A1 promotes tumor invasiveness via integrin-mediated signaling. Similarly, its correlation with high-grade tumors (P < 0.001) and poor survival (OS HR = 1.53) parallels observations in ovarian cancer, where COL11A1 fosters chemoresistance [13]. However, unlike prior studies linking COL11A1 to distant metastasis [14-16], our cohort showed no M-stage association (P = 0.580), suggesting BLCA-specific regulatory mechanisms.

COL11A1 as an immune microenvironment regulator

The robust correlation between COL11A1 and immune infiltration - particularly macrophages (R = 0.650), Th1 cells (R = 0.464), and NK cells (R = 0.433) - echoes findings in lung adenocarcinoma, where collagen XI recruits immunosuppressive myeloid cells [17]. Paradoxically, while Th1/NK cells typically signify antitumor immunity, their coexistence with COL11A1-high tumors and poor prognosis suggests a dysfunctional immune milieu. This aligns with Chen et al.'s report of COL11A1-driven TGF-β activation, which polarizes macrophages toward an immunosuppressive M2 phenotype [18, 19].

Limitations and future directions

Despite rigorous cross-dataset validation, our study has limitations. First, the retrospective

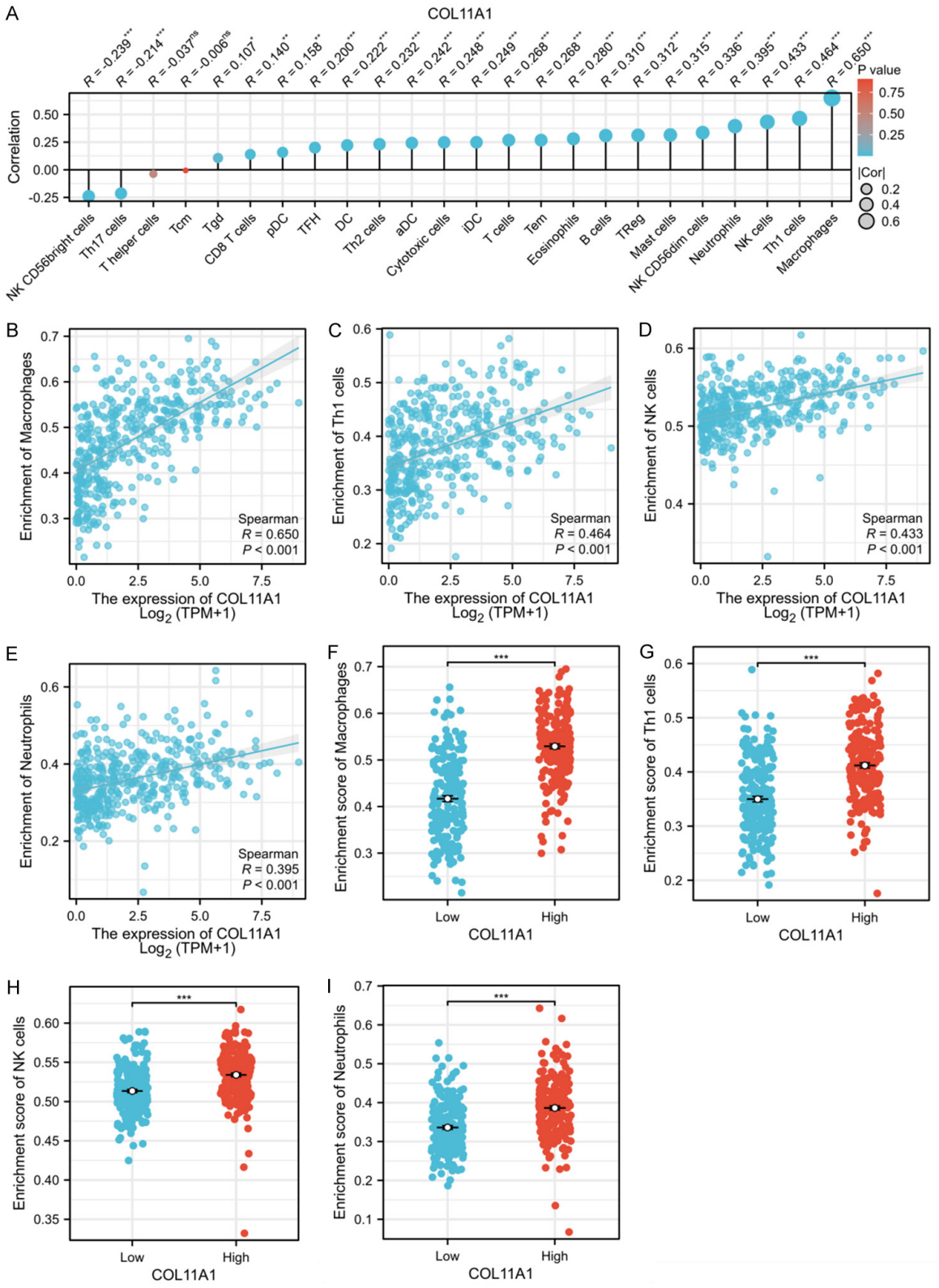

Figure 4. Relationship between COL11A1 expression and immune infiltration in the BLCA microenvironment. A. Correlation between the relative abundance of 24 immune cells and COL11A1 expression. The size of the dots indicates the absolute value of Spearman's correlation coefficient R. B-E. Correlation between COL11A1 expression and infiltration levels of macrophages, Th1 cells, NK cells, and neutrophils. F-I. Correlation between high and low COL11A1 expression and the infiltration levels of macrophages, Th1 cells, NK cells, and neutrophils. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

design and limited normal controls (n = 28) may introduce selection bias. Second, while ssGSEA revealed immune correlations, spatial transcriptomics or multiplex IHC is needed to resolve whether COL11A1-enriched immune cells localize to invasive fronts or tumor cores, a critical determinant of therapeutic response [20]. Third, the absence of functional validation (e.g., CRISPR knockdown models) precludes causal claims about COL11A1's mechanistic role.

Conclusion

COL11A1 emerges as a pivotal biomarker for BLCA, bridging tumor progression and immune evasion. Its prognostic value across subgroups (e.g., N0/M0 patients) highlights its utility in risk stratification. Future studies should elucidate COL11A1's interplay with ECM-immune crosstalk and evaluate COL11A1-targeted therapies (e.g., monoclonal antibodies) in combination with immune checkpoint inhibitors.

Disclosure of conflict of interest

None.

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