Article

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FABP6 is a New Diagnostic and Prognostic Marker for Bladder Cancer

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Purpose: Recent studies have shown that fatty acid-binding protein 6 (*FABP6*) is not only a risk factor for digestive tract tumors, but also a diagnostic marker for digestive tract tumors. This study aimed to extend our understanding by investigating the potential significance of *FABP6* in urinary tract tumors, particularly its role in the bladder cancer progression. We aimed to assess whether *FABP6* influences bladder cancer progression through immune cell interactions.

Methods: Utilizing data from the cancer genome atlas (TCGA) database, the association between *FABP6* expression level and clinical data of bladder cancer was analyzed. This investigation aimed to determine the feasibility of *FABP6* as a marker gene for the diagnosis and prognosis of bladder cancer. Additionally, the correlation between *FABP6* and immune cells in bladder cancer was analyzed.

Results: *FABP6* was highly expressed in bladder cancer ($p < 0.05$). The overall survival (OS), progression-free interval (PFI) and disease-specific survival (DSS) in the high *FABP6* expression group were higher than those in the low *FABP6* expression group (all $p < 0.05$). The expression of *FABP6* was negatively correlated with the infiltration of Th2 cells, macrophages, and Th1 cells (all $p < 0.05$). Conversely, the expression level of *FABP6* was positively correlated with the infiltration of NK CD56^{bright} cells (all $p < 0.05$).

Conclusion: *FABP6* emerges as a promising prognostic marker for bladder cancer. *FABP6* may have an impact on the disease progression of bladder cancer by interacting with different types of immune cells in bladder cancer.

Keywords: bladder cancer; *FABP6*; biomarker; TCGA; immune cell

Introduction

Bladder cancer is one of the most prevalent malignancies in the urinary system and ranks among the top ten malignancies worldwide [1]. The incidence and mortality rate of bladder cancer have been on the rise in recent years [2]. While some biological markers have been identified to aid in diagnosing and targeting bladder cancer [3–5], their clinical application has been limited by low specificity. In the era of precision medicine, the quest for more specific targets associated with bladder cancer is imperative to promote a robust theoretical foundation for targeted therapeutic interventions [6].

Fatty acid-binding protein 6 (*FABP6*), predominantly expressed in the ileum and known as ileal bile acid-binding protein, is an intracellular transporter of bile acids in ileal epithelial cells. Additionally, it plays a crucial role in the catalytic and metabolic processes of cholesterol, contributing significantly to the maintenance of homeostasis of hepatoenteric circulating bile acids [7]. Notably, recent investigations have proposed *FABP6* as a potential biomarker for colorectal cancer due to its elevated expression levels [8]. Given its close association with digestive tract tumors, our team was intrigued by the prospect of *FABP6* playing a pivotal role in urinary tract tumors, particularly bladder cancer.

In this study, we aimed to explore the association between *FABP6* and clinical indicators of bladder cancer, assessing its association with immune cell types and elucidating the signaling pathways implicated in bladder cancer progression. Leveraging the cancer genome atlas (TCGA) bladder cancer database, we analyzed differential *FABP6* expression levels, investigated correlations between *FABP6* expression level and clinical indices and analyzed immune cell types in bladder cancer, and explored the underlying biological mechanisms of *FABP6* regulation of bladder cancer progression through pathway enrichment analysis.

Materials and Methods

Data Acquisition and Preprocessing

The RNAseq data for the the cancer genome atlas-Bladder urothelial carcinoma (TCGA-BLCA) project were acquired and organized using the Xiantao Academic Online website (https://www.xiantaozi.com/). The RNAseq data processed through the Spliced Transcripts Alignment to a Reference (STAR) method were downloaded. No data filtering policies were employed in this study. The data were processed using the log2 transformation (value + 1). The dataset included 412 samples from bladder cancer and 19 samples from adjacent paracancerous tissues.

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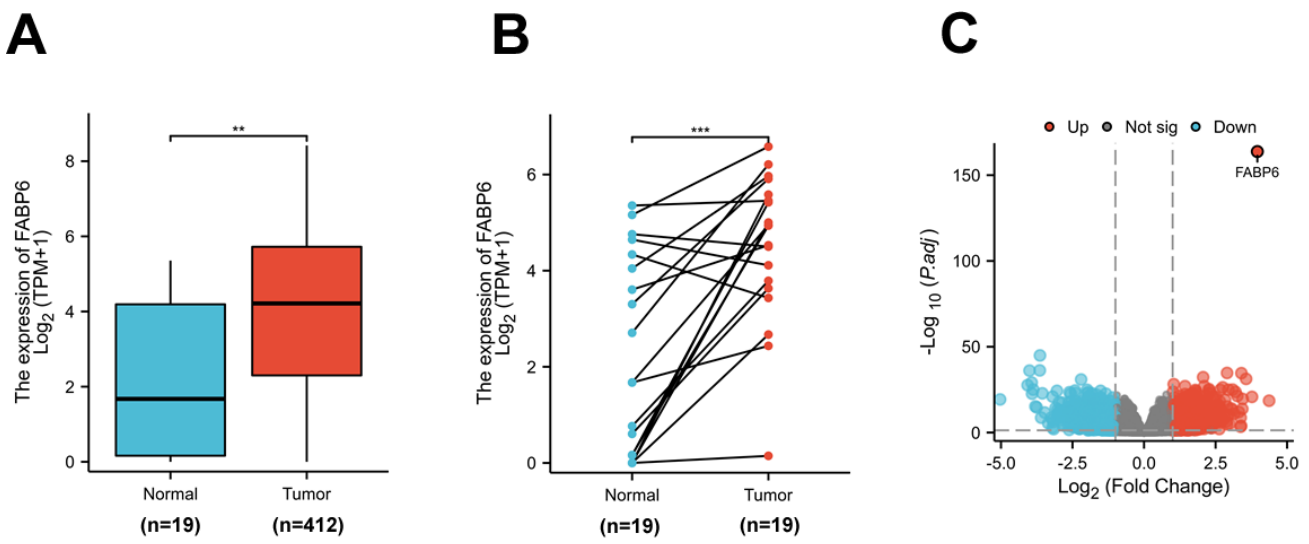

Fig. 1. Differences in fatty acid-binding protein 6 (*FABP6*) expression in bladder cancer and normal tissue. (A) Expression levels of *FABP6* in bladder cancer and normal tissues (p value = 0.0012). (B) Expression levels of *FABP6* in paired bladder cancer and normal tissue (p value = 0.0002). (C) Volcano plot illustrating the expression of FABP*6* in bladder cancer. TPM, transcripts per kilobase million. $^{**}p < 0.01$; $^{***}p < 0.001$.

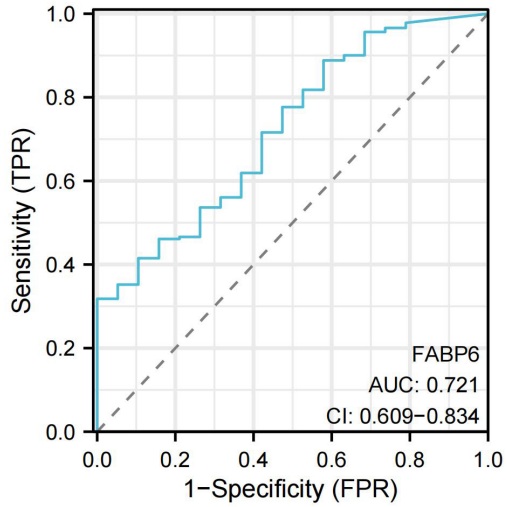

Fig. 2. Analysis of *FABP6* effectiveness in bladder cancer diagnosis using diagnostic receiver operating characteristic (ROC) curve. The x-axis represents the false positive rate (FPR), and the y-axis represents the true positive rate (TPR). AUC, receiver operating characteristic curve; CI, confidence interval.

Differential Analysis of FABP6 Expression

The paired sample *t*-test was selected for statistical analysis to assess the differential expression of *FABP6*, and the ggplot2 package (version 3.3.6, MSN, Redmond, WA, USA) was used for visualization. The volcano plot was generated using the ggplot2 package (version 3.3.6, MSN, Redmond, WA, USA) to visualize the differential analysis results.

Diagnostic Receiver Operating Characteristic (ROC) Curves, Survival Prognosis, and Regression Analysis

Diagnostic ROC, aimed at assessing the predictive accuracy efficiency of a variable, was performed using the pROC package (version 1.18.0, MSN, Redmond, WA, USA). The results were visualized using ggplot2 (version 3.3.6, MSN, Redmond, WA, USA). Survival package (version 3.3.1, MSN, Redmond, WA, USA) was employed for the proportional risk hypothesis test, and survival regression was fitted. The results were visualized using the survminer package and ggplot2 package (version 3.3.6, MSN, Redmond, WA, USA). If the samples in the single factor met the set p-value threshold, they were included in the multi-factor Cox model. The prognostic data utilized in this study were sourced from the article [9]. Preceding the Cox regression analysis, the data were filtered by removing normal + removing no clinical information + removing duplicates. In addition, in cases where the data included infinite values, the values were treated as missing. Before the univariate analysis, samples with missing data in the outcome and time columns were removed.

Correlation Analysis of FABP6 and Clinical Features

To further analyze the correlation between *FABP6* and clinical features, we filtered the downloaded RNAseq data according to the method of removing normal + removing no clinical information + removing duplicates. The data processing method employed was log2 (value + 1). Subsequently, an appropriate statistical method was chosen for correlation analysis based on data characteristics. Additionally, if the data contained infinite values, the values were treated as missing. The strategy of handling missing values was not uniformly applied across variables.

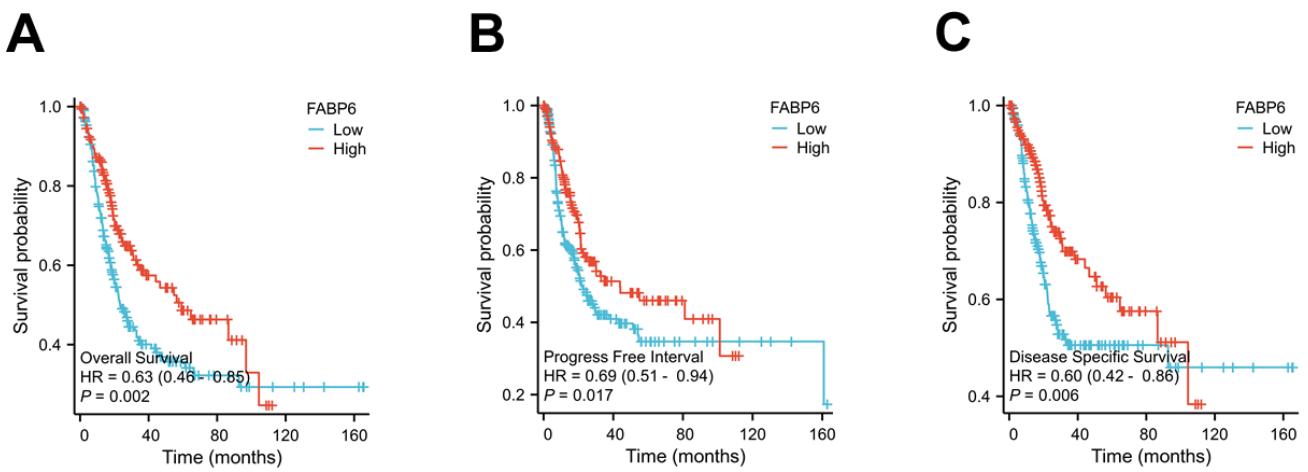

Fig. 3. Analysis of the relationship between *FABP6* expression level and disease prognosis. (A) Comparative analysis between *FABP6* expression levels and overall survival (OS). (B) Comparative analysis of *FABP6* expression level and progression-free interval (PFI). (C) Comparative analysis of *FABP6* expression level and disease-specific survival (DSS). HR, Hazard Ratio.

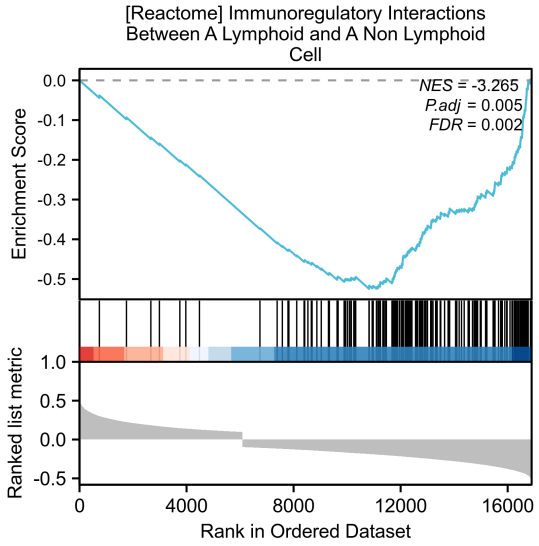

Fig. 4. Gene set enrichment analysis (GSEA) of *FABP6*-related genes. *p.* adjust < 0.05 and Simultaneous false discovery rate (FDR) (q-value) <0.25, indicating statistical significance. NES, Normalized Enrichment Score.

Gene Set Enrichment Analysis (GSEA) of FABP6 and Its Related Genes

GSEA entails utilizing genes from a predefined gene set in the Molecular Signatures Database (MSigDB) to evaluate the distribution trend of genes in the phenotypic correlation ranking, thereby elucidating their contribution and correlation to the phenotype [10]. The specific methodology involves converting the ID of the molecules in the input data using the org.Hs.eg.db package, followed by clusterProfiler package (version 4.4.4, MSN, Redmond, WA, USA) for GSEA analysis.

Relationship between FABP6 and Immune Cells

The association between *FABP6* and immune cells within the bladder cancer microenvironment was further examined through Spearman correlation analysis. The findings were visually represented using a lollipop chart generated with the ggplot2 package (version 3.3.6, MSN, Redmond, WA, USA).

Statistical Methods

The R software (version 4.2.1, MSN, Redmond, WA, USA), was used for the analysis of the aforementioned methods. The xiantao academic platform (https://www.xiantaozi.com) was utilized for data processing, and the results were visualized using the GGplot2 package (version 3.3.6, MSN, Redmond, WA, USA).

Results

Expression Difference of FABP6

Notably, *FABP6* exhibited elevated expression levels in bladder cancer (Fig. 1A). A more in-depth examination of *FABP6* expression in 19 cases of bladder cancer and 19 matched normal tissues revealed a consistently high expression of *FABP6* in bladder cancer tissues (Fig. 1B). The observations were supported by the volcano plot, illustrating a significant overexpression of *FABP6* in bladder cancer (Fig. 1C).

FABP6 is an Effective Marker for Bladder Cancer

The diagnostic efficacy of *FABP6* in bladder cancer diagnosis was analyzed through the analysis of the ROC curve. The area under the curve for *FABP6* predicting positive results was predicted to be 0.721, indicating that *FABP6* has a certain predictive effect on the diagnosis of bladder cancer. Consequently, *FABP6* emerges as a potential biomarker for bladder cancer diagnosis (Fig. 2). Cox

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Table 1. Cox univariate and multivariate analysis of overall survival (OS) in bladder cancer patients.

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
FABP6	405		0.030		
Low	202	Reference		Reference	
High	203	0.720 (0.534–0.969)	0.030	0.742 (0.381–1.447)	0.382
Pathologic T stage	371		0.050		
T1	3	Reference		Reference	
T2 & T3 & T4	368	9077433.8726 (0.000–Inf)	0.994	12392307.4471 (0.000–Inf)	0.999
Pathologic N stage	363		<0.001		
N0	236	Reference		Reference	
N1 & N2 & N3	127	2.255 (1.645–3.091)	<0.001	1.191 (0.556–2.550)	0.653
Pathologic M stage	206		0.007		
M0	195	Reference		Reference	
M1	11	3.283 (1.569–6.870)	0.002	0.720 (0.185–2.798)	0.636
Primary therapy outcome	349		<0.001		
SD & CR	259	Reference		Reference	
PR & PD	90	4.809 (3.416–6.769)	<0.001	4.371 (1.956–9.767)	<0.001
Gender	405		0.510		
Female	106	Reference			
Male	299	0.895 (0.645–1.242)	0.507		
Age	405		0.006		
≤70	227	Reference		Reference	
>70	178	1.518 (1.130–2.038)	0.006	1.047 (0.527–2.079)	0.895
Histologic grade	402		0.074		
Low grade	21	Reference		Reference	
High grade	381	2.887 (0.714–11.668)	0.137	5150465.5858 (0.000–Inf)	0.997
Subtype	400		0.017		
Non-Papillary	269	Reference		Reference	
Papillary	131	0.658 (0.462–0.938)	0.021	1.231 (0.521–2.910)	0.636
Lymphovascular invasion	278		<0.001		
No	129	Reference		Reference	
Yes	149	2.202 (1.514–3.203)	<0.001	2.162 (0.920–5.079)	0.077
Smoker	392		0.147		
No	109	Reference			
Yes	283	1.287 (0.908–1.824)	0.156		
Radiation therapy	379		0.965		
No	358	Reference			
Yes	21	0.984 (0.484–2.004)	0.965		

SD, stable disease; CR, complete response; PR, partial response; PD, progressive disease.

regression results revealed that the overall survival (OS), progression-free interval (PFI), and disease-specific survival (DSS) in the *FABP6* high-expression group were significantly higher than in the *FABP6* low-expression group ($p < 0.05$) (Fig. 3A–C).

In the Cox univariate regression model, the expression difference of *FABP6*, TNM stage, primary treatment outcome, age, pathological grade, tumor subtype, and lymphovascular infiltration were further analyzed. A total of 406 tumor samples were analyzed by Cox regression after filtering the data by removing normal + removing no clinical information + removing duplicates. Notably, one sample missed time or outcome data. Therefore, before the univariate analysis, the missing samples in the outcome and time columns were removed, and finally 405 samples were included in the analysis. The strategy for handling missing values involved addressing missing variables after univariate analysis and before multi-factor analysis. Further, multivariate analysis indicated that the primary treatment outcome was an independent prognostic factor for OS in patients with bladder cancer (Table 1).

Correlation of FABP6 with Clinical Indicators

Following data filtration by removing normal + removing no clinical information + removing duplicate data, 406 tumor samples were included in the analysis. Moreover, in instances where the data contained infinite values,

Table 2. Correlation of *FABP6* with clinical features.

Characteristics n	Low expression of *FABP6* 203	High expression of *FABP6* 203	*p*-value
Pathologic N stage, n (%)			0.144
N0	112 (30.8%)	124 (34.1%)	
N1 & N2 & N3	71 (19.5%)	57 (15.7%)	
Pathologic T stage, n (%)			0.978
T1	1 (0.3%)	2 (0.5%)	
T2 & T3 & T4	188 (50.5%)	181 (48.7%)	
Pathologic M stage, n (%)			0.048
M0	74 (35.9%)	121 (58.7%)	
M1	8 (3.9%)	3 (1.5%)	
Pathologic stage, n (%)			0.478
Stage I	0 (0%)	2 (0.5%)	
Stage II & Stage III & Stage IV	202 (50%)	200 (49.5%)	
Primary therapy outcome, n (%)			0.046
SD & CR	118 (33.8%)	141 (40.4%)	
PD & PR	52 (14.9%)	38 (10.9%)	
Histologic grade, n (%)			<0.001
High grade	201 (49.9%)	181 (44.9%)	
Low grade	1 (0.2%)	20 (5%)	
Subtype, n (%)			<0.001
Non-Papillary	153 (38.2%)	116 (28.9%)	
Papillary	46 (11.5%)	86 (21.4%)	
Lymphovascular invasion, n (%)			0.733
No	68 (24.4%)	61 (21.9%)	
Yes	76 (27.2%)	74 (26.5%)	
Gender, n (%)			0.175
Female	59 (14.5%)	47 (11.6%)	
Male	144 (35.5%)	156 (38.4%)	
Age, n (%)			0.841
≤70	113 (27.8%)	115 (28.3%)	
>70	90 (22.2%)	88 (21.7%)	
Smoker, n (%)			0.003
No	41 (10.4%)	68 (17.3%)	
Yes	154 (39.2%)	130 (33.1%)	

n, Number of samples.

the values were treated as missing, employing a strategy where missing variables were not uniformly handled.

The results revealed that the differential expression of *FABP6* was associated with the pathologic M stage ($p = 0.048$), primary therapy outcome ($p = 0.046$), histologic grade ($p < 0.001$), subtype ($p < 0.001$), and smoker status ($p = 0.003$) (Table 2).

GSEA Analysis of FABP6 and Its Related Genes

The findings of the GSEA analysis revealed that the gene sets associated with *FABP6* are predominantly enriched in immunoregulatory interactions between lymphoid and non-lymphoid cells in the reactome pathway database (Fig. 4). This observation suggests a potential role of *FABP6* in immunomodulatory activities among various cell types in the tumor microenvironment of bladder cancer.

Correlation Analysis of FABP6 and Immune Cell

Spearman correlation analysis suggested that *FABP6* was negatively correlated with Macrophages, Th2 cells and Th1 cells. *FABP6* was positively correlated with NK CD56^{bright} cells (Fig. 5).

In addition, based on the expression levels of *FABP6*, we applied the single-sample GSEA (ssGSEA) algorithm to analyze the relationship between *FABP6* and immune cell infiltration. The results demonstrated that the infiltration of macrophages, Th1 cells, Th2 cells, neutrophils, T cells, Treg cells, NK CD56^{dim} cells, ADC cells, and B cells in the group with high *FABP6* expression was lower than in the group with low *FABP6* expression. Conversely, the infiltration of NK CD56^{bright} cells in the high *FABP6* expression group was higher than in the low *FABP6* expression group (Fig. 6).

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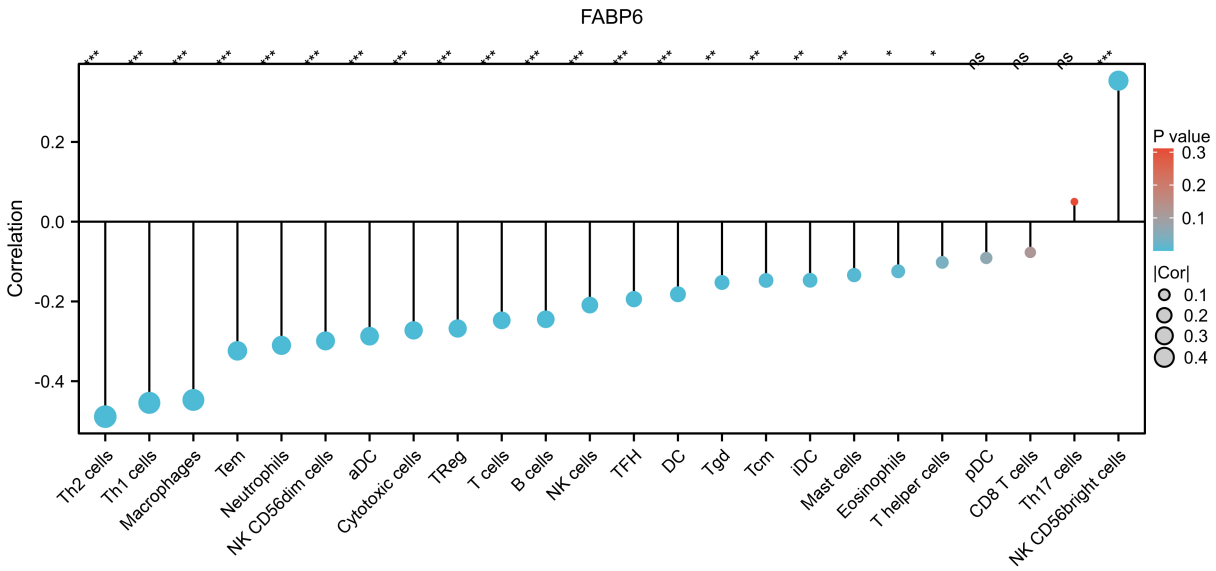

Fig. 5. Correlation analysis of *FABP6* and immune cells. ns, no significant; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

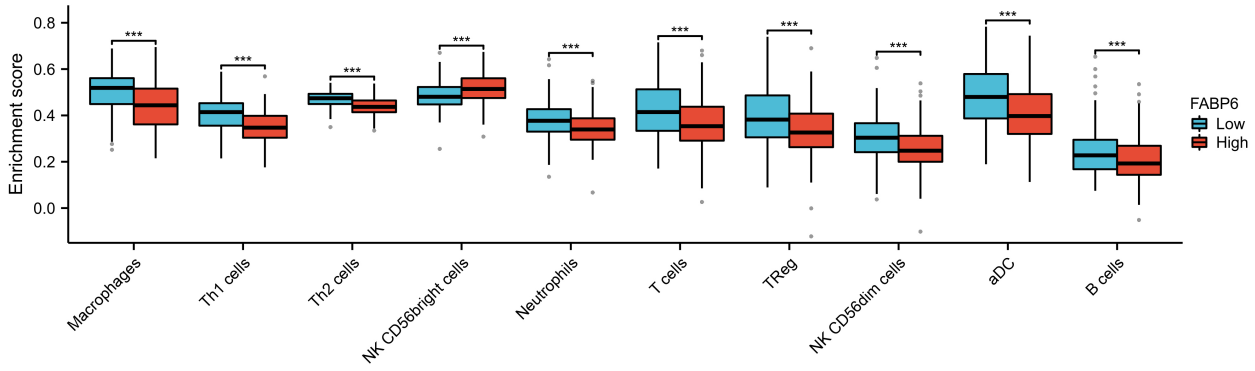

Fig. 6. Differences in immunoinfiltration results between *FABP6* expression groups. Statistical analysis was conducted using the Wilcoxon rank sum test (***$p < 0.001$).

Discussion

The fatty acid-binding protein (*FABP*) family encompasses various subtypes, each exhibiting distinct tissue specificities. *FABP* family has the highest expression in liver, intestine, heart, fat cells and other tissues involved in lipid metabolism. The *FABP* family plays a key role in fatty acid metabolism [11]. Intracellular fatty acid movement is a complex activity that affects many aspects of cell function. *FABP6*, synthesized in the liver and subsequently excreted into the small intestine alongside bile acids, is essential for efficient dietary fat digestion and absorption [12,13].

Notably, *FABP6* is a risk factor and diagnostic marker for colon cancer [8,14]. Intrigued by its potential role in bladder cancer, our team explored existing literature, uncovering two noteworthy studies. One study elucidated the role of *FABP6* in bladder cancer cell progression through transwell experiments, xenotransplantation animal models, and knockdown of *FABP6* expression [15]. Another study constructed a prognostic model based on 11 genes, including *FABP6*, derived from four cohorts. *FABP6* emerged as a protective gene in this model, holding promise as a biomarker for predicting OS in bladder cancer patients. This model is suitable for risk stratification in bladder cancer patients and facilitates the implementation of individualized treatment [16].

To unravel the biological mechanisms of *FABP6* in bladder cancer, bioinformatics analyses were conducted. The original data were derived from the bladder urothelial carcinoma project in the TCGA database. The study primarily focused on downloading RNAseq data and clinical information. The findings indicated a high expression of *FABP6* in bladder cancer, aligning with the recent research. That study observed cell cycle arrest in *FABP6*-knocked out bladder cancer cells and suggested that *FABP6* may be a potential target for bladder cancer cell progression [15]. Furthermore, the ROC curve analysis indicated that *FABP6* may have a potential predictive value in the diagnosis of bladder cancer.

Additionally, our study indicated that the OS, PFI, and DSS in the high *FABP6* expression group were significantly

higher than in the low *FABP6* expression group. The results from multivariate analysis further highlighted the primary treatment outcome as an independent prognostic factor for OS in bladder cancer patients. The expression level of *FABP6* in bladder cancer correlates with pathological M stage, primary treatment outcome, histological grade, subtype, and smoking status. In summary, *FABP6* is closely associated with various clinical indicators in bladder cancer patients. In particular, it is closely related to the clinical stage, tissue type and treatment effect of patients with bladder cancer, ultimately affecting the prognosis of patients. Consequently, further exploration of *FABP6* is warranted.

The biological mechanism underlying the influence of *FABP6* on bladder cancer is of interest to our team. GSEA results revealed the potential of *FABP6*-related gene sets in immunomodulatory interactions between lymphocytes and non-lymphocytes. Based on the GSEA results, we investigated the correlation between *FABP6* and immune cells in bladder cancer.

Currently, immunotherapy is a focal point in bladder cancer research. However, substantial heterogeneity exists in the efficacy of immunotherapy across different individuals, underscoring the need for further basic research on bladder cancer immunotherapy. Despite the growing interest in this area, reports on the relationship between *FABP6* and immune cells in bladder cancer remain limited. A more in-depth analysis of the relationship between *FABP6* and immune cells in bladder cancer will provide a foundation for advancing bladder cancer immunotherapy research.

Our study suggested that the infiltration of macrophages, Th1 cells, Th2 cells, neutrophils, T cells, Treg cells, NK $CD56^{dim}$ cells, ADC cells, and B cells in the high *FABP6* expression group was lower compared to the low *FABP6* expression group. Conversely, the infiltration of NK $CD56^{bright}$ cells in the high *FABP6* expression group was higher than in the low *FABP6* expression group. Recent evidence highlights the unique role of human NK cell subpopulation in innate immune responses, producing high levels of immunomodulatory cytokines in addition to expressing adhesion molecules and cytokines *in vitro* [17,18]. Current studies also implicate anti-inflammatory M2 macrophages, such as tumor-associated macrophages, promoting tumor growth and invasion [19]. Imbalances in various T lymphocyte subsets, including Th1 cells, Th2 cells, and Treg cells, are associated with immune dysfunction [20]. Consequently, *FABP6* may influence the disease course of bladder cancer by affecting the type or quantity of immune cell infiltration. However, the specific mechanism of immunomodulatory action requires more in-depth experimental research in the future.

Several limitations exist in our study. Firstly, our conclusions are based on database-driven bioinformatic analyses, necessitating additional data sets for validation. Secondly, some of the findings of our study, such as the interrelationships between immune cells, need to be further explored in molecular biology experiments.

Conclusion

In summary, our study indicates a high expression of *FABP6* in bladder cancer, suggesting its potential as an effective prognostic marker for bladder cancer. *FABP6* may have an impact on the disease progression of bladder cancer by interacting with different types of immune cells in bladder cancer.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the first author if needed.

Author Contributions

YY designed the research study. YY and ZL performed the research. JL and MY analyzed the data. YY finalized the version to be published. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.cer.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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