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Investigation of the prognostic impact of proline-rich protein 11 (PRR11) transcription levels in early-stage bladder cancer

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MAIN POINTS

- PRR11 is expressed in bladder cancer.
- A negative correlation was observed between PRR11 transcription levels and survival outcomes in patients with early-stage bladder cancer.
- PRR11 transcription levels in bladder cancer may be a useful biomarker for predicting prognosis.

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ABSTRACT

Aim: To investigate proline-rich protein 11 (PRR11) transcription levels and its prognostic effect in early-stage (non-metastatic) bladder cancer.

Materials and Methods: Thirty-one patients diagnosed with early-stage (non-metastatic) bladder cancer were included in the study. Tumor tissues of the patients at the time of diagnosis were obtained from the pathology laboratory, PRR11 transcription levels were analyzed, and "median fold change" values for PRR11 transcription levels were obtained. According to the median PRR11 transcription level determined from these values, the patients were divided into two groups (n = 16 and n = 15). The demographic and clinicopathological characteristics of the patients were examined, and the survival outcomes of the two groups were compared.

Results: The determined median PRR11 transcription level was 1.386 (range: 0.135- 2.016). In the patient group with a median PRR11 transcription level ≤1.381 (n=16), median disease-free survival (mDFS) was 19 months (95% CI: 2.1-48.4 months); in the group with >1.381 (n=15), mDFS was 11 months (95% CI: 7.5-14.4 months). In the group with ≤1.381, median overall survival (mOS) was 27 months (95% CI: 4.1-58.3 months), and in the group with >1.381, mOS was 14 months (95% CI: 8.1-19.8 months).

Conclusion: Our study revealed a negative correlation between PRR11 transcription level and survival outcomes in patients with early-stage bladder cancer. The PRR11 transcription level may be a prognostic marker in patients with early-stage bladder cancer. More comprehensive, prospective, and randomized controlled trials are needed.

Keywords: Biomarker, Bladder cancer, Prognosis, Proline-rich protein 11

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INTRODUCTION

Bladder cancer is one of the most common malignancies of the genitourinary tract [1,2]. Recently, immune checkpoint inhibitors have started to find a place in the treatment, especially in advanced-stage bladder cancer patients. Tolerance of ICI is better compared to chemotherapy, especially in elderly patients with comorbidities. Although ICI is a good treatment alternative, overall response rates are 15-20% [3]. At the same time, chemotherapy response rates also vary [4]. At this point, new biomarkers are needed to select treatment, predict treatment response, and assess prognosis.

Proline-rich 11 (PRR11) is a gene on chromosome 17q22-23 encoding a proline-rich protein [5,6]. PRR11 expression is reported to be increased in different types of cancer, such as ovarian carcinoma [7], breast cancer [8], non-small cell lung cancer [9,10], colorectal cancer [11], esophageal cancer [12], and pancreatic cancer [13].

PRR11 expression has a role in the cell cycle and may contribute to the oncogenic process [6]. Zhang et al. demonstrated increased PRR11 expression in the late S phase of the cell cycle, which remained high until just before mitotic telophase. Suppression of PRR11 resulted in cell cycle arrest

in the late S phase. In addition, suppression of PRR11 caused a significant delay in G2/M progression and induced apoptosis [14].

We aimed to investigate PRR11 transcription levels and their prognostic effect in early-stage (non-metastatic) bladder cancer.

MATERIALS AND METHODS

Study design

Thirty-one early-stage (non-metastatic) muscle-invasive bladder cancer patients followed up in our center between December 2014 and June 2021 were evaluated retrospectively. The transcription levels of PRR11 expression in the tumor tissues of patients at diagnosis were analyzed. The values derived from the analysis were also compared with each other, and a median fold change value was calculated for each patient. These values were subsequently recorded.

The demographic data, including gender, age, smoking history, comorbidities, and clinical variables such as treatment methods and survival outcomes for disease-free survival (DFS) and overall survival (OS) of all the patients were documented. Disease-free survival was defined as the duration between diagnosis and the date of recurrence or death. Overall survival is defined as the duration between diagnosis and the date of death or the last known date of being alive.

RNA extraction, cDNA synthesis, and qRT-PCR

Total RNA was obtained from tissues using the DiaRex® Total RNA Extraction kit (Cat No: TR-0877, Diagen, Turkey). In summary, 5-30 mg of tissue was homogenized in a 1.5 mL tube, followed by extraction in accordance with the manufacturer's protocol, resulting in the acquisition of 30-50 µl of Total RNA. Total RNAs were preserved at -80°C until the study was conducted.

Preserved samples were thawed on ice, and RNA measurements (Colibri Titertek Berthold, Germany) were performed to stabilize RNA concentrations before cDNA processing. Then, cDNA synthesis was started using SOLIScript® RT cDNA synthesis KIT (SolisBIODYNE, Estonia). After all the content was prepared, it was loaded into a conventional PCR device (ThermoFisher Veriti, America). As for the PCR protocol, reverse transcription was performed at 50°C for 5 minutes. At the end of the reaction, the enzyme was inactivated at 85 °C for 5 minutes. After inactivation, cDNA products were stored at -20 °C.

SolisFAST® SolisGreen® qPCR Mix (no ROX), 5X (SolisBIODYNE, Estonia) was used to determine gene expression levels. For the 1X PCR reaction, the total volume consisted of 4 µl master mix, 5 µl mixB (containing 0.3mM forward and reverse primers), 6 µl dH2O, and 5 µl cDNA, making the total volume 20 µl. The reaction was carried out on a real-time PCR device (BioRAD CFX-96, Germany), first denaturation 95 oC 5 min, 45 repetitions 95 oC 5 sec, 55 oC(mir-34a/mir-146a/mir-181) 57 oC(U6/mir-148a) was applied as 30 seconds (reading). Relative mRNA expression levels obtained for specific genes via the device were determined using the 2-ΔΔCt method with the R package (qpcrtools 1.0.1, ggpubr 0.6.0, dplyr 1.1.4, tidyverse 2.0.0, car 3.1-2).

Statistical analysis

Descriptive statistics were used to examine the demographic and clinicopathological characteristics of the patients. Categorical data was analyzed using the chi-square test.

The median follow-up time was determined utilizing the reverse Kaplan-Meier method. Survival analyses of median DFS (mDFS) and median OS (mOS) were performed using the Kaplan-Meier method, and possible prognostic factors were compared using the log-rank test. A p-value below 0.05 was deemed statistically significant. All statistical analyses were conducted via the IBM SPSS Version 21.0 (Armonk, NY: IBM Corp.).

RESULTS

Patients' demographic and Clinicopathological characteristics

The study included 31 patients with early-stage (non-metastatic) bladder cancer. Of the patients, 28 (90.3%) were male and 3 (9.7%) were female. The mean age of the patients was 71.9 (±10.04). Nineteen (61.2%) of the patients were active smokers, 6 (19.3%) were ex-smokers, and 6 (19.5%) of the patients had no smoking history (Table 1). Four (2.9%) of the patients were initially diagnosed with non-muscle invasive bladder cancer and were subsequently diagnosed with muscle-invasive bladder cancer. The remaining 27 (97.1%) patients were initially diagnosed with muscle-invasive bladder cancer.

Table 1. Patients' baseline demographic and clinicopathologic characteristics.

	Total (n=31)
Age (years), (±SD)	71.9 (±10.04)
Sex M/F (n)	28/3
Comorbidities, n (%)	
Hypertension	6 (19.3)
Diabetes Mellitus	6 (19.3)
Lung Disease	4 (12.9)
Treatment modality, n (%)	
Neoadjuvant Therapy	8 (25.8)
Adjuvant Therapy	7 (22.5)
Definitive CRT	16 (51.7)
Smoking History, n (%)	
Active smoker	19 (61.4)
Ex-smoker	6 (19.3)
Non-smoker	6 (19.3)
Stage, n (%)	
Stage 1	0
Stage 2	21 (67.7)
Stage 3A	8 (25.8)
Stage 3B	2 (6.5)

CRT: Chemoradiotherapy.

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Table 2. Patients' survival outcomes according to PRR11 transcription levels.

	All patients (n=31)	PRR11 transcription level ≤1.381 (n=16)	PRR11 transcription level >1.381 (n=15)	p value
DFS, months, median 95% CI	14 3.4-24.5	19 2.1-48.4	11 7.5-14.4	0.486
OS, months, median 95% CI	27 4.1-60.07	27 4.1-58.3	14 8.1-19.8	0.514

DFS: Disease-free survival, OS: Overall survival, CI: Confidence interval.

Twenty-one (67.7%) patients were stage II, 8 (25.8%) patients were stage IIIA, and 2 (6.5%) patients were stage IIIB. Six of the patients had positive lymph nodes at the time of diagnosis. When the treatment modalities were examined, 7 (22.5%) patients received adjuvant chemotherapy after radical cystectomy and pelvic lymph node dissection. Eight (25.8%) patients received neoadjuvant chemotherapy followed by radical cystectomy and pelvic lymph node dissection. Sixteen (51.7%) patients received definitive chemoradiotherapy (Table 1). In some of the patients who received definitive chemoradiotherapy, this treatment was chosen because the patients did not accept surgery.

PRR11 transcription levels

PRR11 transcription levels were analyzed in 31 patients with early-stage (non-metastatic) bladder cancer tumor tissues. All transcription levels were analyzed within themselves, and median fold change values were obtained. These values ranged between 0.135 and 2.016 (Figure 1). The median PRR11 transcription level value in the entire patient group was 1.381. Patients were examined in 2 groups according to the median value of 1.381. There were 16 patients with a PRR11 transcription level of ≤1.381 and 15 with a level of>1.381. The two groups were similar in terms of age, gender, smoking history, stage at diagnosis, and treatment modalities.

Survival analysis

The median follow-up time was 25 months (min: 3-max: 84). mDFS was 14 months (95% CI: 3.4-24.5 months), and mOS was 27 months (95% CI: 4.1-60.07 months) for all patients. In the patient group with a median PRR11 transcription level value ≤1.381 (n=16), mDFS was 19 months (95% CI: 2.1-48.4 months); in the group with >1.381 (n=15), mDFS was 11 months (95% CI: 7.5-14.4 months) (Figure 2a). In the group with ≤1.381, mOS was 27 months (95% CI: 4.1-58.3 months), and in the group with >1.381, mOS was 14 months (95% CI: 8.1-19.8 months) (Figure 2b) (Table 2).

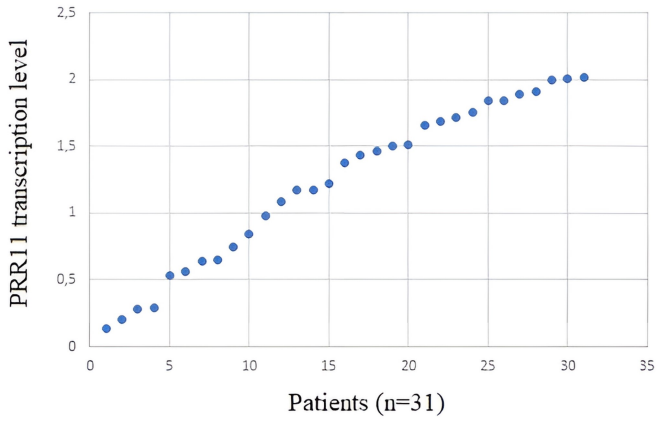

Figure 1. Distribution of PRR11 transcription levels of patients.

DISCUSSION

Bladder cancer is a heterogeneous condition characterized by a high recurrence rate; nevertheless, there is no reliable predictor for directing therapy. Recent studies have established models for bladder cancer related to DNA methylation-dependent genes or those involving immune genes, and these models may provide prognostic insights [15,16].

PRR11 expression is being investigated as a possible prognostic and/or therapeutic target in different types of cancer. However, the studies are insufficient to reach a definitive conclusion on this issue. Studies showing the role of PRR11 in the cell cycle, particularly in the late S phase, indicate that the amount of PRR11 increases and that silencing PRR11 delays G2-M progression and stimulates apoptosis [14], suggesting that PRR11 may have an oncogenic effect.

In our study, PRR11 transcription levels were analyzed in patients diagnosed with early-stage bladder cancer, and their effect on prognosis was investigated. Our study showed a negative correlation between PRR11 transcription levels and survival outcomes. However, p-values did not reach statistical significance, probably due to the small number of patients; a numerical difference was detected between the two groups in both DFS and OS. When the literature was reviewed, some studies investigated PRR11 expression in bladder cancer, and these studies have similar findings to our research.

A study based on online databases investigated the possible oncogenic and prognostic role of PRR11 expression in bladder cancer. This study showed that PRR11 was significantly expressed in bladder cancer patients, and patients with high expression had the worst prognosis. Tumor mutation burden (TMB) and immune cell infiltration were also examined in these patients. It was determined that PRR11 expression was positively correlated with TMB and levels of immune cell infiltration [17]. In a study conducted using data from The Cancer Genome Atlas (TCGA), which analyzed non-small

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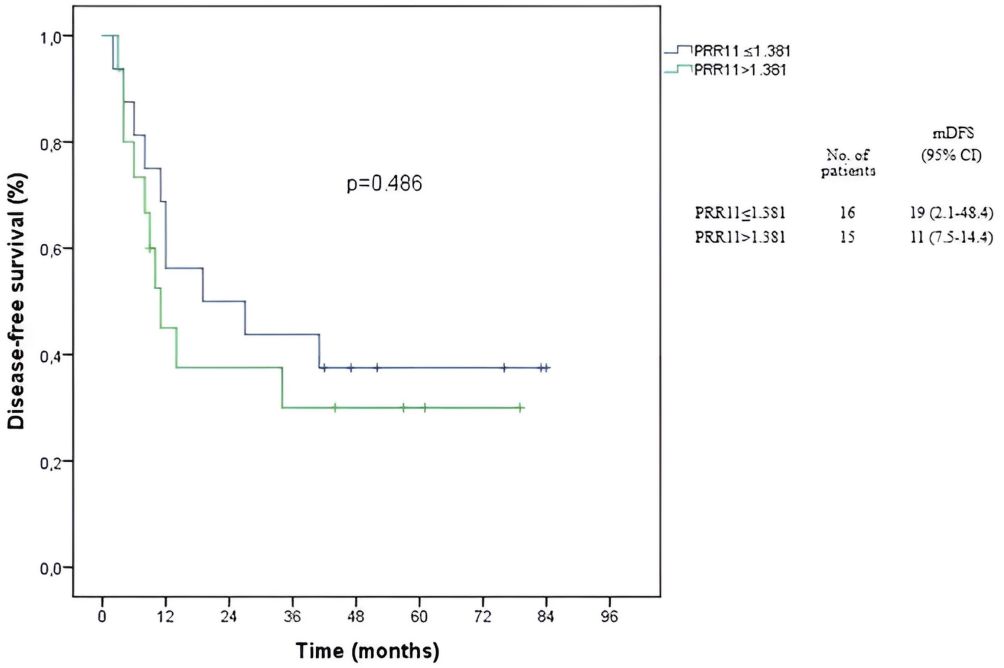
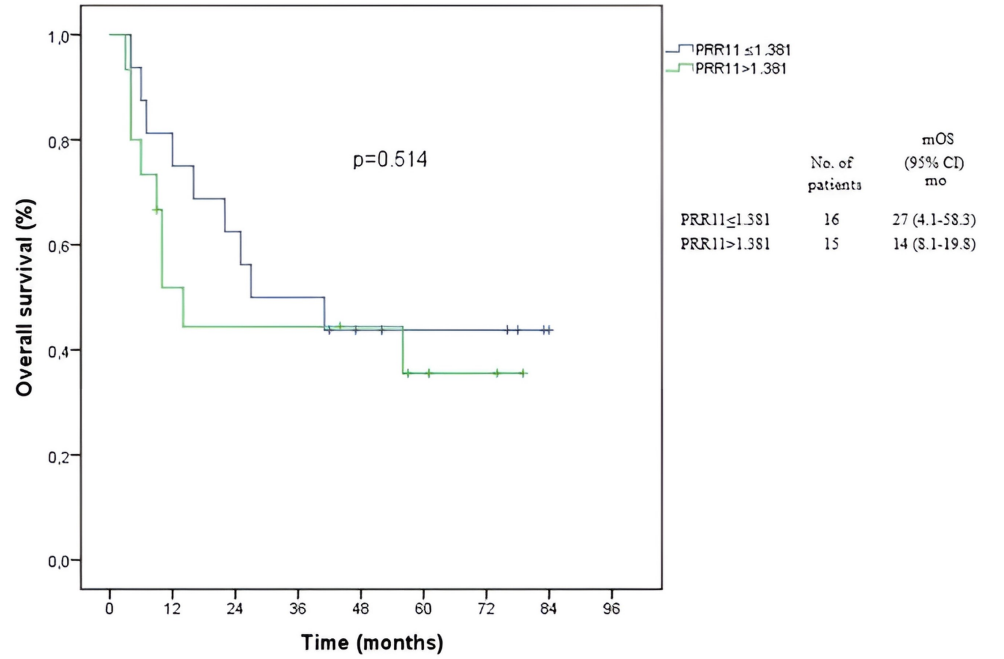


(a) Kaplan Meier curve for mDFS according to PRR11 transcription levels.



(b) Kaplan Meier curve for mOS according to PRR11 transcription levels.

Figure 2. Distribution of PRR11 transcription levels of patients.

cell lung cancer (NSCLC) and bladder cancer patient tissues, smoking-related genes and the PRR11 gene were evaluated as potential immunotherapeutic targets. As a result of the study, it was suggested that PRR11 could be a potential prognostic gene in both non-small cell lung cancer (NSCLC) and bladder cancer. Additionally, it was demonstrated that PRR11 plays a crucial role in regulating programmed death ligand 1 (PD-L1) by interacting with spindle apparatus coiled-coil protein 1 (SPDL1) [18]. Jiaxing Lin et al. investigated prognostic genes in bladder cancer patients using four cohorts from TCGA and Gene Expression Omnibus databases. They detected 8 risk-increasing genes and 3 protective genes. One of the 8 genes that increase risk is PRR11. According to the risk scale created by these genes, patients with high-risk scores have the worst prognosis [19].

Bladder cancer is a heterogeneous disease, and new biomarkers that may be useful in predicting treatment selection, treatment response, and/or prognosis are needed. Various genes,

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such as PRR11 and other biomarkers, are still being investigated. Due to the heterogeneous structure of the tumor, response rates to ICIs and chemotherapies vary, making it challenging to predict treatment selection and prognosis. PRR11 gene expression is being investigated as a possible biomarker in bladder cancer, as in many different types of cancer, especially since it varies in different phases of the cell cycle and is considered potentially oncogenic. Although there is no precise data with current information, it can be used as a targetable biomarker in the future. Alternatively, when evaluated as a poor prognostic factor, it can guide approaches such as more aggressive treatment options or closer follow-up.

CONCLUSION

The PRR11 transcription level may serve as a prognostic marker in patients with early-stage bladder cancer. Our study found a negative correlation between PRR11 transcription level and survival outcomes. However, the number of patients was insufficient to generalize the results. In addition, the analysis performed showed PRR11 expression indirectly through transcription levels. PRR11 may be a useful marker pending validation in larger cohorts and multivariate modeling. More comprehensive, prospective, and randomized controlled trials are needed.

Ethics Committee Approval: The research received approval from the hospital's ethics committee (Dr. Abdurrahman Yurtaslan Oncology Health Application and Research Center Clinical Research Ethics Committee, Decision no: 2020-05/631).

Informed Consent: No new tissue samples were taken; archival tissue was used.

Peer-review: Externally peer-reviewed.

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