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Expression and Clinical Relevance of p53 and BCL-2 in Bladder Cancer

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Экспрессия и клиническая значимость p53 и BCL-2 при раке мочевого пузыря

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Introduction. Bladder cancer is a prevalent malignancy with high recurrence and progression rates. Molecular markers like p53 and BCL-2 are implicated in tumor behavior — p53 in tumor suppression and BCL-2 in apoptosis inhibition — yet their clinical significance remains unclear. This study investigates the expression of p53 and BCL-2 in bladder cancer tissues and their associations with key clinical and pathological features to inform more personalized patient management.

Materials and Methods. Immunohistochemical analysis was performed on bladder cancer tissue samples to assess p53 and BCL-2 expression levels. Correlations with tumor grade, invasiveness, gender, age, and smoking status were examined.

Введение. Рак мочевого пузыря — распространенное злокачественное новообразование с высокими показателями рецидива и прогрессии. Такие молекулярные маркеры, как p53 и BCL-2 влияют на развитие опухоли (p53 подавляет развитие опухоли, а BCL-2 ингибирует апоптоз), однако их клиническая значимость остается неясной. В данном исследовании проводится изучение экспрессии p53 и BCL-2 в тканях рака мочевого пузыря и их взаимосвязь с ключевыми клиническими и патологическими особенностями с целью разработать более персонализированный подход к лечению пациентов.

Материалы и методы. На образцах тканей рака мочевого пузыря было проведено иммуногистохимическое исследование для оценки уровней экспрессии p53 и BCL-2. Мы изучили корреляции со степенью злокачественности опухоли, инвазивностью, полом, возрастом пациентов и статусом курения.

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Results. p53 expression was significantly higher in cancerous tissues than in normal tissues ($p < 0.00001$) and was associated with high-grade tumors ($p = 0.03156$). No significant difference in BCL-2 expression was observed between cancerous and normal tissues ($p = 0.19706$). No significant correlations were found between p53 and BCL-2 expression or with the clinical factors.

Conclusion. The overexpression of p53 in high-grade bladder cancer tissues highlights its potential role as a biomarker for tumor aggressiveness, whereas BCL-2 shows limited prognostic relevance.

Keywords: p53; BCL-2; bladder cancer; biomarkers; tumor grade, clinical correlation

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Результаты. Экспрессия p53 была значительно выше в раковых тканях по сравнению со здоровыми тканями ($p < 0,00001$) и ассоциировалась с опухолями высокой степени злокачественности ($p = 0,03156$). Клинически значимых различий в экспрессии BCL-2 между раковой и здоровой тканью не выявлено ($p = 0,19706$). Существенных корреляций между экспрессией p53 и BCL-2 или с клиническими факторами обнаружено не было.

Заключение. Повышенная экспрессия маркера p53 в опухолях мочевого пузыря высокой степени злокачественности подчеркивает его потенциальную роль в качестве биомаркера агрессивности опухоли, тогда как BCL-2 демонстрирует ограниченную прогностическую значимость.

Ключевые слова: p53; BCL-2; рак мочевого пузыря; биомаркеры; степень злокачественности опухоли, клиническая корреляция

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Introduction

Bladder cancer represents a substantial global health issue, ranking as one of the most prevalent malignancies worldwide[1]. According to the GLOBOCAN 2022 data, bladder cancer is now the 9th most commonly diagnosed cancer globally, with an estimated 614,298 new cases in 2022, reflecting a 7.1 % increase from previous years[1, 2]. Bladder cancer is characterized by a wide range of clinical and pathological presentations, which can be broadly categorized into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). This classification is crucial as it directly influences treatment strategies and prognostic outcomes [3].

The etiology of bladder cancer is indeed multifaceted, involving a combination of genetic predispositions and environmental risk factors. Several somatic mutations occur in genes such as TP53, FGFR3, and PIK3CA, which are crucial for regulating cell growth and division may be associated with bladder carcinogenesis. There are rare instances where inherited mutations at GSTM1 can elevate the risk due to impaired detoxification of carcinogens[4]. Cigarette smoking is one of the most significant risk factors, accounting for approximately 50 % of bladder cancer cases. Smokers have a four to five times greater risk compared to non-smokers[4, 5]. Despite advances in treatment modalities such as transurethral resection, chemotherapy, immunotherapy, and radical cystectomy, bladder cancer is characterized by high recurrence and progression rates[4, 5].

Recent literature has significantly advanced the understanding of the molecular mechanisms underlying bladder cancer, particularly focusing on key biomarkers such as p53 and BCL-2. These proteins are crucial in tumor biology, influencing cancer progression and patient outcomes. The tumor suppressor protein p53 and the anti-apoptotic protein BCL-2 play contrasting roles in bladder cancer progression and prognosis. Mutations in the p53 gene, frequently observed in bladder cancer, are associated with higher tumor grades, advanced disease stages, and poor prognoses due to their correlation with aggressive disease phenotypes[6–8]. Acting as a transcription factor, p53 regulates DNA repair and apoptosis, making it a critical marker for disease progression and a potential therapeutic target, though further prospective studies are needed to clarify its clinical management role[6–8]. Conversely, BCL-2, known for inhibiting programmed cell death, is often overexpressed in cancer, contributing to treatment resistance[6, 9]. Interestingly, its expression may be reduced in more aggressive bladder cancer forms, suggesting its potential as a marker for less aggressive disease [9, 10]. The interplay between p53 and BCL-2 significantly impacts tumor cell survival and therapeutic responses [9, 10].

Despite progress in understanding bladder cancer's molecular mechanisms, the roles of p53 and BCL-2 concerning clinical, demographic, and histopathological factors remain unclear. While p53 mutations are linked to aggressive disease and BCL-2 overexpression to treatment resistance, their interactions and clinical implications require further exploration. Limited research has addressed their differential expression in normal compared to cancerous tissues and associations with tumor grade, invasiveness, and patient demographics. This study investigates p53 and BCL-2 expression in bladder cancer tissues and their links to clinical variables,

aiming to clarify their potential as diagnostic and prognostic markers. We particularly compare p53 and BCL-2 expression levels in bladder cancer tissues versus adjacent normal tissues, and examine the associations of these markers with tumor grade, invasiveness, smoking status, age, and gender. Moreover, we explore the potential correlation between p53 and BCL-2 expression.

Materials and Methods

Study Design and Sample Analysis

This retrospective study included 67 formalin-fixed, paraffin-embedded bladder tissue samples, comprising 46 tumor tissues and 21 non-tumorous tissues, archived at Keçiören Training and Research Hospital between 2023 and 2024. Tumor samples were histopathologically confirmed as bladder cancer, while the non-tumorous tissues were obtained from patients initially suspected of having bladder lesions but were later diagnosed with conditions such as chronic inflammation, normal histology, squamous metaplasia, follicular cystitis, or chronic cystitis.

Inclusion criteria for the tumor group included: (1) histopathological diagnosis of urothelial carcinoma of the bladder; (2) availability of sufficient archived tissue for immunohistochemical analysis; and (3) complete clinical data including age, gender, smoking status, tumor grade, and invasion status. For the non-tumorous group, inclusion required: (1) absence of malignant findings in histopathological evaluation; and (2) tissue obtained during diagnostic cystoscopy or resection for suspected bladder pathology.

Samples with (1) insufficient or degraded tissue samples; (2) previous history of bladder malignancy in the non-tumorous group; (3) presence of mixed or variant histologies other than urothelial carcinoma; and (4) missing or incomplete clinical data were excluded from the study.

The analysis examined associations between tumor grade, smoking status, gender, age, and histopathological characteristics. Tumor grade was classified as low or high based on the WHO histopathological grading system. Tissue invasion was categorized as invasive or noninvasive. Smoking status was grouped as smoker, non-smoker, or ex-smoker. Gender was classified as male or female, and age was stratified into four groups: 40–49, 50–59, 60–69, and ≥70 years.

Histopathological Evaluation

Histopathological examination plays a pivotal role in characterizing tumor properties, ensuring precise diagnosis, classification, and prognostic assessment. Tissue specimens obtained during surgical procedures are immediately fixed in 10 % buffered formalin to maintain structural integrity. These specimens are processed by embedding in paraffin, and thin sections measuring 4 μm are cut using a microtome. The sections are mounted onto glass slides and stained with hematoxylin and eosin (H & E) to examine tissue architecture and cellular morphology. Additionally, immunohistochemical (IHC) staining is conducted to evaluate the expression of key proteins, including BCL-2, and TP53. This multifaceted analysis provides critical molecular and histological insights, facilitating tailored treatment decisions and prognostic predictions.

Immunohistochemical Analysis

Immunohistochemical staining was employed to determine BCL-2, and TP53 protein levels in bladder tissue samples. After fixation in formalin, tissue sections were deparaffinized in xylene and rehydrated through graded ethanol, followed by a distilled water rinse for 3 minutes. To inhibit endogenous peroxidase activity, the sections were treated with 3 % hydrogen peroxide in methanol for 10 minutes. Antigen retrieval was achieved using a 0.01M citrate buffer (pH 6.0) heated in a pressure cooker for 3 minutes.

After antigen retrieval, sections were washed in Tris-buffered saline (TBS) containing 0.15M sodium chloride and 0.05M Tris-HCl (pH 7.6) to maintain stability. A blocking solution (SuperBlock, SHP125; ScyTek Laboratories, UT, USA) was applied to minimize non-specific binding. Primary antibodies were diluted as per the manufacturer's protocols and applied to the sections: anti-BCL-2 (Boster, USA; dilution 1 : 750), and anti-p53 (M00001-4, Boster Biological Technology; dilution 1 : 200). Following incubation, sections were treated with a biotinylated secondary antibody (SHP125; ScyTek Laboratories) and a streptavidin-HRP complex.

Subsequent to TBS washes, diaminobenzidine (DAB) was used as a chromogen to detect peroxidase activity, and nuclei were lightly counterstained with hematoxylin for better visualization. Slides were dehydrated through ethanol, cleared in xylene, and mounted for microscopic examination. A blinded pathologist assessed the staining under a light microscope. Enzymatic staining intensity was scored as 0 (negative), 1 (weak), 2 (moderate), or 3 (strong). For p53, the percentage of positively stained nuclei was recorded, with samples classified as positive if more than 10 % of nuclei displayed staining (fig. 1).

Statistical Analysis

Statistical analyses were conducted using R software (Version 4.3.2, R Foundation, Vienna, Austria). Clinical and demographic data were summarized with descriptive statistics. Continuous variables were expressed as mean ± standard deviation along with their range (minimum–maximum), while categorical variables were represented as frequencies and percentages. The Shapiro-Wilk test was

employed to assess the normality of numerical variables, and the Levene test was used to evaluate homogeneity of variances. For group comparisons involving normally distributed variables meeting parametric assumptions, the Student's t-test or one-way ANOVA was utilized, depending on the number of groups. For non-normally distributed data or when parametric assumptions were not met, the Mann-Whitney U test was applied. Chi-square for indepencency was examined the association between categorical variables. Correlations between continuous variables were analyzed using Spearman's rank correlation. Statistical significance was set at a p-value of less than 0.05.

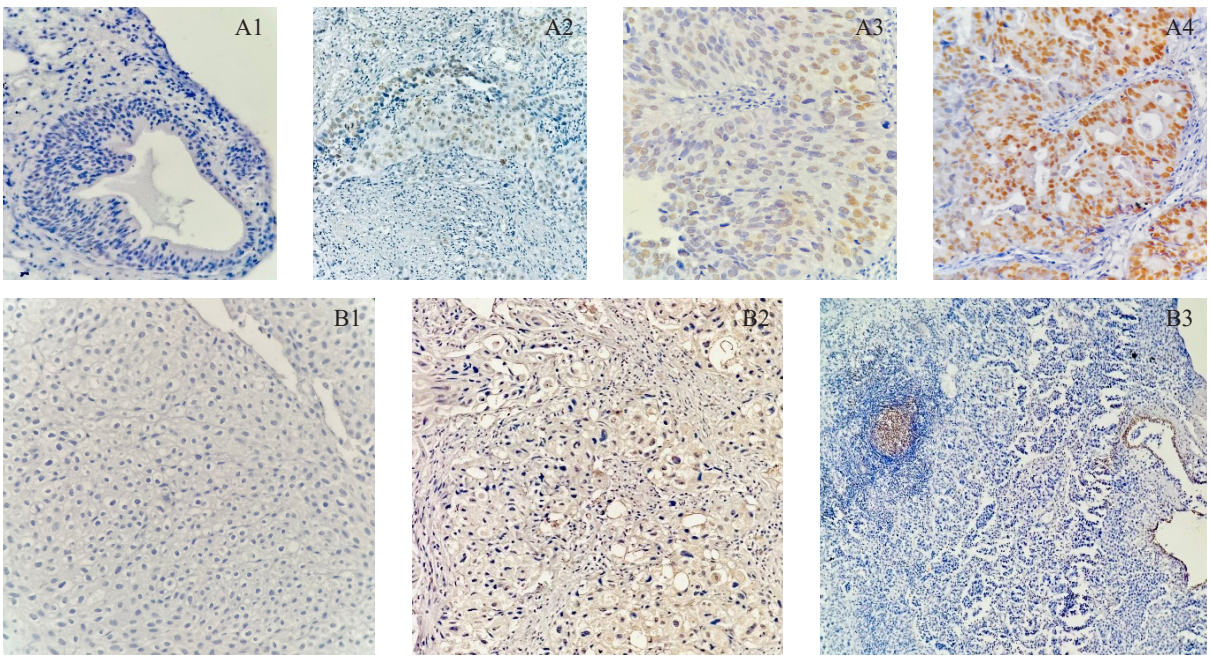

Fig. 1. (A1) Microscopic view of a sample in which p53 protein expression is not observed (Negative). (A2) General microscopic image of a specimen marked positive (+1) for p53 protein expression. (A3) General microscopic image of a specimen marked positive (+2) for p53 protein expression. (A4) General microscopic image of a specimen marked positive (+3) for p53 protein expression. (B1) Microscopic view of a sample in which Bcl-2 protein expression is not observed. (B2) General microscopic image of a specimen marked positive (+1) for Bcl-2 protein expression. (B3) General microscopic image of a specimen in which control and normal tissues were positively marked for Bcl-2 protein expression, whereas tumor portions of the same tissue were negatively marked

Table 1. Demographic characteristics and their relationship with BCL-2 and P53 expression

Gender	Biomarkers	Positive n	Negative n	P-value
Male	BCL-2	3	38	0.9
Female		1	4	
Male	P53	32	9	0.5
Female		5	0	
Age category				
Middle age 40-65	BCL-2	2	22	0.6
Old age >65		2	20	
Middle age 40-65	P53	18	6	0.5
Old age >65		19	3	
Smoking status				
Smoker	BCL-2	4	37	1
Non smoker		0	5	
Smoker	P53	32	9	0.1
Non smoker		5	0	
Overall				
Cancerous	BCL-2	4	42	0.03
Healthy		6	15	
Cancerous	P53	37	9	< 0.00001
Healthy		3	18	

Results

The study analyzed 46 cancerous tissue samples and 21 normal tissue samples. The age of cancer patients ranged from 42 to 94 years, with a mean age of 65.2 ± 11.5 years. The male-to-female ratio was 41:5. Smoking status among cancer patients included 41 participants with a history of smoking, either active smokers or former smokers, and 5 nonsmokers. Among cancer cases, 11 were classified as low-grade, and 35 as high-grade. Moreover, 20 patients (43.5 %) were diagnosed at stage 1, 21 patients (45.6 %) at stage 2, and 5 patients (10.9 %) at stage 3 of cancer progression. Additionally, 12 cases were noninvasive, while 34 were invasive. In the normal tissue group, participant ages ranged from 28 to 89 years, with a mean age of 54.6 ± 16.6 years. The male-to-female ratio was 9:12, and

Table 2. Cancer stages and grade distribution of patients and their relationship with BCL-2 and P53 expression

Cancer stage		0	1	2	3	P-value
Stage 1	BCL-2	19	1	0	0	0.00008
Stage 2		21	0	0	0	
Stage 3		2	3	0	0	
Stage 1	P53	6	11	1	2	0.00025
Stage 2		3	4	8	18	
Stage 3		0	0	2	4	
Cancer grade						
Low grade	BCL-2	10	1	0	0	0.9
High grade		32	3	0	0	
Low grade	P53	4	5	1	1	0.03
High grade		5	10	9	11	
Cancer invasiveness						
Noninvasive	BCL-2	12	0	0	0	0.6
Invasive		30	4	0	0	
Noninvasive	P53	4	4	1	3	0.4
Invasive		5	11	9	9	
Overall						
Cancerous	BCL-2	42	4	0	0	0.03
Healthy		15	6	0	0	
Cancerous	P53	9	15	10	12	< 0.0001
Healthy		18	3	0	0	

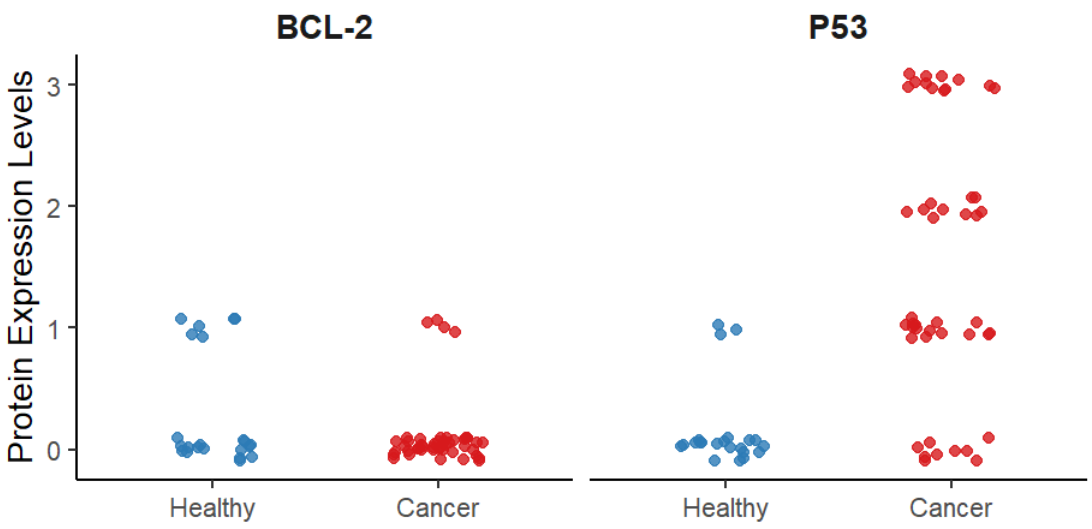

Fig. 2. BCL-2 and P53 protein expression levels in healthy and cancerous bladder tissues

smoking statuses included 12 participants with a history of smoking and 9 nonsmokers.

A significant difference in P53 expression was observed between cancerous and normal tissues ($p < 0.00001$). However, no significant difference in BCL-2 expression was found ($p = 0.19706$) (table 1 & fig. 2). Furthermore, no correlation was observed between BCL-2 and P53 expression levels in either cancerous ($rs = 0.25852$, $p = 0.08278$) or normal tissues ($rs = 0.34426$, $p = 0.12647$). Gender was not significantly associated with the expression of BCL-2 in cancerous ($p = 0.65994$) or normal tissues ($p = 0.30302$), nor with P53 expression in cancerous ($p = 0.33204$) or normal tissues ($p = 0.61708$). Age and gender differences between groups with varying expression levels were insignificant ($p > 0.2$). Smoking history did not significantly influence P53 and BCL-2 expression levels in cancerous compared to normal tissues ($p > 0.5$). The expression levels of both BCL-2 ($p = 0.5552$) and P53 ($p = 0.27134$) did not vary significantly based on cancer invasiveness.

A significant difference in P53 expression was noted among patients with different cancer grades ($p = 0.03156$). However, no significant difference was observed for BCL-2 expression ($p = 0.99202$) (Table 2). A comparative analysis of BCL-2 and TP53 immunohistochemical staining scores across cancer stages revealed distinct expression patterns. Chi-square analysis indicated a significant difference in BCL-2 expression across stages ($\chi^2 = 18.92$, $p = 0.00008$) (table 2). Fisher's exact test revealed no significant difference between stages 1 and 2 ($p = 0.488$), but significant differences between stage 1 and stage 3 ($p = 0.016$), and stage 2 and stage 3 ($p = 0.0038$), suggesting altered BCL-2 expression in advanced-stage patients. Analysis confirmed a significant association between TP53 scores and cancer stage ($\chi^2 = 25.72$, $p = 0.00025$) as well (Table 2). Fisher's exact test further identified significant differences in scores 1 and 3 between stage 1 and stage 2 ($p = 0.0014$ and $p = 0.0013$), and between stage 1 and stage 3 ($p = 0.0237$ and $p = 0.0129$), while no significant differences were found between stages 2 and 3. In essence, the findings indicate a distinct upregulation or altered pattern of BCL-2 expression in Stage 3, while TP53 expression tends to increase from Stage 1 to Stage 2 and then remains high in Stage 3.

Discussion

This study describes the expression profiles of p53 and BCL-2 in bladder cancer patients. The findings underscore the significant role of p53 in differentiating cancerous from normal tissues and stratifying cancer grades and stages. In contrast, BCL-2 expression remains relatively stable in early stages, but shows a marked alteration in Stage 3, possibly indicating its involvement in advanced tumor survival or resistance to apoptosis. By systematically examining these markers in relation to tumor grade, stage, smoking history, and demographics, the study offers a nuanced perspective on their implications. Moreover, the interplay between p53 and BCL-2 is explored, suggesting their combined potential as prognostic markers and identifying directions for further investigation. These findings contribute to expanding biomarker research in bladder cancer, paving the way for integrated approaches to patient care.

Existing literature corroborates the elevated expression of p53 in cancerous bladder tissues, which may be associated with high-grade tumors and aggressive phenotypes, suggesting its prognostic value [6, 11]. Additionally, p53 overexpression correlates with tumor recurrence and progression, reinforcing its predictive relevance in tumor characteristics such as grade and stage [6, 12, 13]. However, conflicting findings indicate that p53 may not consistently predict tumor progression or recurrence, particularly under certain positivity thresholds [11]. However, the lack of significant variation in p53 expression based on demographic or clinical factors emphasizes its limited applicability in broader clinical contexts. This complexity underscores the need for further research to refine thresholds for p53 expression, establish its clinical applications, and clarify its reliability as a biomarker for bladder cancer outcomes.

This study suggests that BCL-2 has limited prognostic relevance in bladder cancer, consistent with prior reports indicating the low expression of BCL-2 in bladder cancer tissues, with only a minority of cases showing positivity, limiting its prognostic potential [14, 15]. While some studies have linked low BCL-2 expression to low-grade tumors, others highlight its predictive value for treatment response, particularly in poor outcomes with neoadjuvant chemotherapy [15, 16]. While p53 is strongly associated with tumor progression and aggressiveness, BCL-2 appears to play a more limited role, primarily related to treatment response rather than tumor grade or invasiveness[9, 17] .

Contradictory findings in some studies suggest potential interactions between p53 and BCL-2 in specific contexts, such as treatment responses or unique tumor microenvironments [17, 18]. Although no significant correlation was observed in this study, the combined evaluation of these markers could offer insights into tumor behavior or therapeutic outcomes in particular circumstances. Further research is required to fully explore these potential interactions, which may hold significance for developing more targeted diagnostic and therapeutic strategies.

Our findings are generally consistent with earlier reports, although larger prospective cohorts or guideline-referenced biomarker panels—such as those proposed by the EAU and NCCN—do not currently incorporate p53 or BCL-2 due to inconsistent predictive validity. Clinically, the overexpression of p53—particularly in high-grade tumors—may support more intensive surveillance strategies or early systemic therapy. Although BCL-2 has limited prognostic impact, its potential role in predicting chemotherapy response could inform neoadjuvant treatment planning in selected cases.

This study has several limitations that should be considered. First, the relatively small sample size limits the generalizability of the findings. A larger, more diverse cohort could provide robust insights into the relationships between p53, BCL-2, and bladder cancer characteristics. Second, reliance on tissue samples from a single institution introduces potential biases related to demographic and clinical factors. Third, the cross-sectional design restricts the ability to establish temporal or causal relationships between biomarker expression and clinical outcomes. Additionally, the lack of stratification by molecular subtypes of bladder cancer may have overlooked variations in biomarker expression across different subtypes. Finally, the study did not assess other relevant molecular markers or genetic factors that could influence bladder cancer progression, limiting the scope of the molecular landscape.

Conclusion

Elevated p53 expression in high-grade bladder cancer suggests its usefulness as an indicator of tumor aggressiveness, whereas BCL-2 appears to have minimal prognostic value. Future research should prioritize prospective, multi-center studies with molecular subtype stratification. Integration of p53 and BCL-2 into multi-marker immunohistochemical panels, alongside markers such as Ki-67 and FGFR3, may provide a more comprehensive prognostic tool.

Conflict of interest
The authors declare no conflicts of interest.

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Compliance with patient rights and principles of bioeth
This study received ethical approval from the Institutional Review Board (IRB) of Bandirma Onyedi Eylul University (Approval No: E-67961857-050.04-167778; Date: 10.12.2024). Participants were thoroughly informed about the study, and written informed consent was obtained. The study was conducted in accordance with ethical guidelines, including the Declaration of Helsinki and its subsequent revisions.

Availability of data and materials
All data supporting the findings of this study are included within the article. Additional raw data are available from the corresponding author upon reasonable request.

Authors' contributions
Selim Öğüt, Pınar Kaygın, Onur Dirican, Abbas Ali Husseini, Gülçin Güler Şimşek: conceptualization, methodology.
Isameel Khan Qadam, Gülçin Güler Şimşek, Selim Öğüt: Experiments. Abbas Ali Husseini, Serap Yesilkir Baydar: formal analysis.
Abbas Ali Husseini, Serap Yesilkir Baydar, Ömer Faruk Bozkurt, Selim Öğüt: data management.
Onur Dirican, Abbas Ali Husseini, Serap Yesilkir Baydar, Selim Öğüt: writing, reviewing, and editing.
All authors have read and approved the final manuscript.

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