ORIGINAL PAPER

FGFR3 mRNA expression in urothelial bladder cancer: associations with tumor phenotype without prognostic impact

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Introduction *FGFR3* (fibroblast growth factor receptor 3) is frequently altered in urothelial carcinoma and has been associated with less aggressive disease, but its prognostic relevance remains uncertain. We evaluated tumor *FGFR3* mRNA expression levels in relation to clinicopathological phenotype and outcomes in bladder cancer.

Material and methods Fresh-frozen tumor tissue from 80 urothelial carcinomas (54 non-muscle-invasive, 26 muscle-invasive) was used for RNA extraction and quantitative PCR. *FGFR3* expression levels were normalized to pooled controls and $\log_{10}$-transformed. Associations with invasiveness, grade, and survival were assessed using logistic and Cox regression, with discrimination quantified by the area under the curve (AUC) and calibration by the Brier score.

Results Higher *FGFR3* expression was independently associated with non-muscle-invasive disease (OR 6.35, 95% CI: 2.14–18.83; p <0.001; AUC 0.74; Brier 0.180) and low grade (OR 5.99, 1.78–20.13; p = 0.004; AUC 0.74; Brier 0.189). *FGFR3* was not associated with overall survival (HR 0.52, 95% CI: 0.25–1.06; p = 0.072). In the NMIBC subset, *FGFR3* was not associated with recurrence-free survival (HR 1.09, 0.37–3.20; p = 0.880). Age (HR 1.03, 0.98–1.09; p = 0.191) and grade (HR 2.16, 0.78–5.94; p = 0.137) were also non-significant.

Conclusions Tumor *FGFR3* mRNA expression was strongly associated with a less aggressive phenotype but showed no independent prognostic value for survival in this cohort. *FGFR3* may support phenotypic assessment at diagnosis, while its prognostic role warrants validation in larger studies.

Key Words: urothelial carcinoma ‹› bladder cancer ‹› *FGFR3* ‹› gene expression ‹› prognosis ‹› biomarkers

INTRODUCTION

Urothelial carcinoma of the bladder (UCB) accounts for the vast majority of bladder cancer cases. Globally, bladder cancer is among the ten most common cancers, with ~614,300 new cases in 2022 and a marked male predominance. Within the bladder, disease ranges from non-muscle-invasive tumors, usually managed endoscopically, to muscle-invasive disease with substantially worse prognosis. Despite established risk stratification based on stage, grade, tumor size, and multiplicity, there remains a clinical need for biomarkers that are inexpensive, reproducible, and applicable at the time of transurethral resection of bladder tumor (TURBT) to refine phenotypic characterization and guide follow-up [1–4]. Fibroblast growth factor receptor 3 (*FGFR3*) is a receptor tyrosine kinase implicated in urothelial tumorigenesis. Activating alterations are common in UCB, particularly in papillary, low-grade,

non-muscle-invasive tumors, and have driven the development of *FGFR3*-targeted agents for selected patients with advanced disease. At the genomic and transcriptomic levels, pathway activation arises through recurrent hotspot mutations (e.g. S249C, R248C, Y373C), occasional *FGFR3–TACC3* fusions and, in some cases, overexpression without coding alterations. These events are enriched in low-grade, papillary non-muscle-invasive bladder cancer (NMIBC) and less frequent in muscle-invasive bladder cancer (MIBC); fusions occur in only a small minority of cases [5–9].

Clinically, the therapeutic relevance of *FGFR3* is established: on 19 January 2024 the US FDA granted full approval to erdafitinib for adults with locally advanced or metastatic UCB harboring susceptible *FGFR3* alterations after prior systemic therapy. Nevertheless, whether tumor *FGFR3* mRNA measured at diagnosis provides independent prognostic information beyond standard clinicopathological variables remains unresolved. Prior studies have reported directionally mixed associations between *FGFR3* expression and outcomes in NMIBC (for example, shorter recurrence-free but better overall survival in T1 cohorts), while pooled analyses more consistently link *FGFR3* mutation, rather than expression, with favorable features [8, 10–12]. We therefore examined *FGFR3* mRNA expression in fresh-frozen bladder cancer tissues in relation to phenotype and survival.

MATERIAL AND METHODS

Study design and tissue samples

This study represents a retrospective analysis of prospectively collected biobank samples. Fresh-frozen tumor tissues were obtained from patients undergoing initial TURBT between January 2021 and June 2023. Immediately after resection, tissue samples were preserved in RNAlater solution and stored at −80°C until molecular analysis.

RNA isolation and quantification

Total RNA was isolated from fresh-frozen tumor tissue using the acid guanidinium thiocyanate–phenol–chloroform extraction method described by Chomczynski and Sacchi, employing TRIzol reagent (Invitrogen, USA), according to the manufacturer's instructions. RNA concentration was measured using a Qubit fluorometer (Thermo Fisher Scientific). Samples with RNA concentrations below 10 ng/μl were excluded from further molecular analysis. RNA integrity was not formally assessed; however, all samples met the predefined concentration criteria and yielded robust amplification profiles in downstream analyses.

Reverse transcription

Complementary DNA (cDNA) synthesis was performed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). For each reaction, 500 ng of total RNA was reverse-transcribed in a final reaction volume of 40 μl using random hexamer primers. Reverse transcription was carried out according to the manufacturer's protocol, with a total synthesis time of approximately 150 minutes. Generated cDNA was stored at −20°C until quantitative PCR analysis.

Quantitative real-time PCR

Quantitative real-time PCR was performed on the StepOne Real-Time PCR System (Applied Biosystems) using SYBR Green-based chemistry. *FGFR3* mRNA expression was quantified relative to the endogenous reference gene *GAPDH* (glyceraldehyde-3-phosphate dehydrogenase). All reactions were performed in duplicate. Melt-curve analysis was conducted to confirm amplification specificity, and no-template controls (NTC) were included in each run. No reverse transcription–negative (no-RT) control reactions were included. Reactions with Ct values ≥36 were excluded from further analysis. Primer sequences and real-time PCR conditions are provided in Suppl. Table 1.

Normalization and expression analysis

Relative gene expression levels were calculated using the ΔΔCt method. GAPDH served as the reference gene for normalization, and pooled normal bladder tissue was used as the calibrator sample. For statistical analyses, *FGFR3* mRNA expression values were $\log_{10}$-transformed.

Clinical data and endpoints

Clinicopathological data, including tumor stage, grade, tumor size, and tumor multiplicity, were obtained from medical records. Overall survival (OS) was defined as the time from TURBT to death from any cause or last follow-up. Recurrence-free survival (RFS) was defined as the time from TURBT to first documented tumor recurrence or last cystoscopic follow-up without evidence of recurrence. Surveillance for tumor recurrence was performed at 3, 6, 12, and 24 months following TURBT. The last follow-up was conducted in June 2025.

Statistical analysis

Associations between *FGFR3* mRNA expression and clinicopathological variables were assessed using regression models appropriate to data type and distribution. Survival analyses were performed using Cox proportional hazards models. Due to incomplete treatment-related information, therapy variables were excluded from the analyses, and a complete-case approach was applied. Given the limited number of outcome events, survival analyses were considered exploratory.

Bioethical standards

The study was conducted in accordance with the Declaration of Helsinki. Tumor samples were obtained from patients treated at the University Clinic for Urology in Skopje, and ethical approval for the study was granted by the Ethics Committee of the University Clinic for Urology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje (IRB No. 03-16/2, January 4, 2021). Written informed consent for genetic analyses was obtained from all patients prior to sample collection.

RESULTS

Patient characteristics

Eighty patients met the inclusion criteria. Most tumors were non-muscle-invasive, and high-grade disease was common. Baseline clinicopathological features, including tumor size, multifocality, and presenting symptoms, are summarized in Table 1. During the follow-up period, 17 patients from the NMIBC subset experienced tumor recurrence, and 31 deaths were recorded in the study cohort.

FGFR3 and tumor phenotype (primary aim)

Higher *FGFR3* mRNA expression (per 1-$\log_{10}$ unit) was independently associated with a less aggressive phenotype (Figure 1). In the model for invasiveness, the odds of being NMIBC rather than MIBC increased with higher *FGFR3* expression (OR = 6.35, 95% CI: 2.14–18.83; p <0.001; Table 2), while age showed no association (OR = 0.99, 0.94–1.05; p = 0.797). In the model for grade, higher expression was associated with low-grade disease (OR = 5.99, 1.78–20.13; p = 0.004; Table 3), again with no age effect (OR = 0.99, 0.94–1.04; p = 0.726). Model discrimination was moderate (AUC 0.74 for both outcomes; Table 4). Results were identical when *FGFR3* alone or *FGFR3* plus age was considered, reflecting the lack of an age effect. ROC curves for *FGFR3* alone are shown in Suppl. Figure 1, with consistent AUC values when MIBC and high grade were set as positive classes. Distributions of *FGFR3* expression by grade and invasiveness are shown in Figure 2.

Table 1. *Patient characteristics. Values are n (%) unless stated. Age is median [IQR]. Smoking categories by pack-years: Never (0), Moderate (1–19), Heavy (≥20). Pathological T stage refers to index TURBT (pTa/pT1/pT2); pT2–pT4 are considered MIBC*

Characteristic	All patients (n = 80)
Age, years – median [IQR]	66 [61–72]
Sex	
Male	65 (81%)
Female	15 (19%)
Invasiveness	
NMIBC	54 (68%)
MIBC	26 (32%)
Concomitant CIS	
Yes	3 (4%)
No	77 (96%)
Grade	
Low	27 (34%)
High	53 (66%)
Pathological stage (T) at index TURBT	
pTa	29 (36%)
pT1	25 (31%)
pT2	26 (32%)
Tumor focality	
Unifocal	60 (75%)
Multifocal	20 (25%)
Tumor size	
<3 cm	31 (39%)
≥3 cm	49 (61%)
Smoking (pack-years)†	
Never (0)	35 (44%)
Moderate (1–19)	31 (39%)
Heavy (≥20)	14 (18%)
Hematuria	
None	3 (4%)
Microscopic	3 (4%)
Gross	74 (92%)
Dysuria	
Yes	58 (72%)
No	22 (28%)

CIS – carcinoma *in situ*; IQR – interquartile range; MIBC – muscle-invasive bladder cancer; NMIBC – non-muscle-invasive bladder cancer

Table 2. *Logistic regression model for invasiveness (NMIBC vs. MIBC) with FGFR3 $\log_{10}$ mRNA expression and age. Outcome coding: MIBC = 1, NMIBC = 0. Odds ratios (OR) >1 indicate higher odds of MIBC; two-sided Wald p-values*

Predictor	OR	95% CI	p-value
FGFR3 mRNA ($\log_{10}$)	6.35	2.14–18.83	<0.001
Age (per year)	0.99	0.94–1.05	0.797

Survival (secondary aim)

In the NMIBC subset (n = 54), *FGFR3* was not associated with recurrence-free survival (HR = 1.09, 95% CI: 0.37–3.20; p = 0.880). Age also showed no significant effect (HR = 1.03, 0.98–1.09; p = 0.191), and high grade was not significant (HR = 2.16, 0.78–5.94; p = 0.137) (Table 5). *FGFR3* was not as-

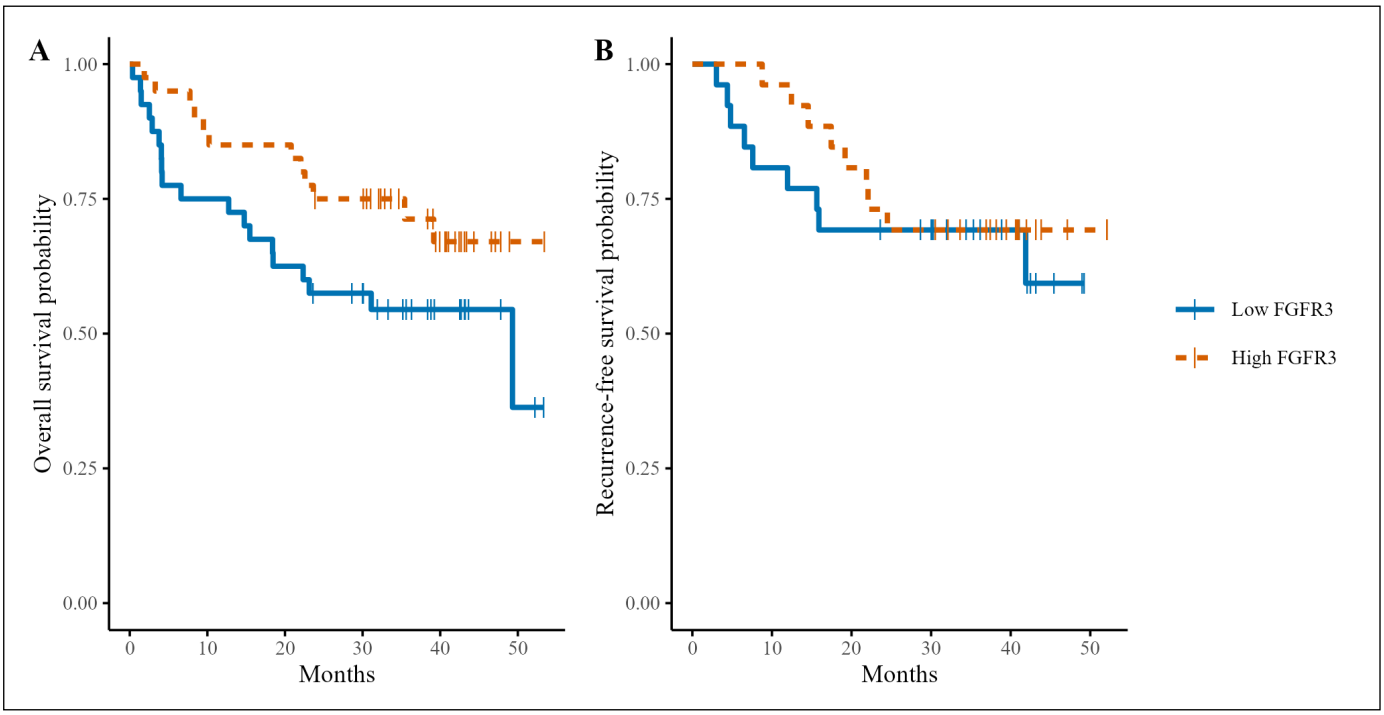


Figure 1. *Kaplan–Meier survival curves stratified by FGFR3 log_{10} mRNA expression (median split).* **A)** *Overall survival (all patients, n = 80).* **B)** *Recurrence-free survival (NMIBC subset, n = 54). Tick marks indicate censored cases.*

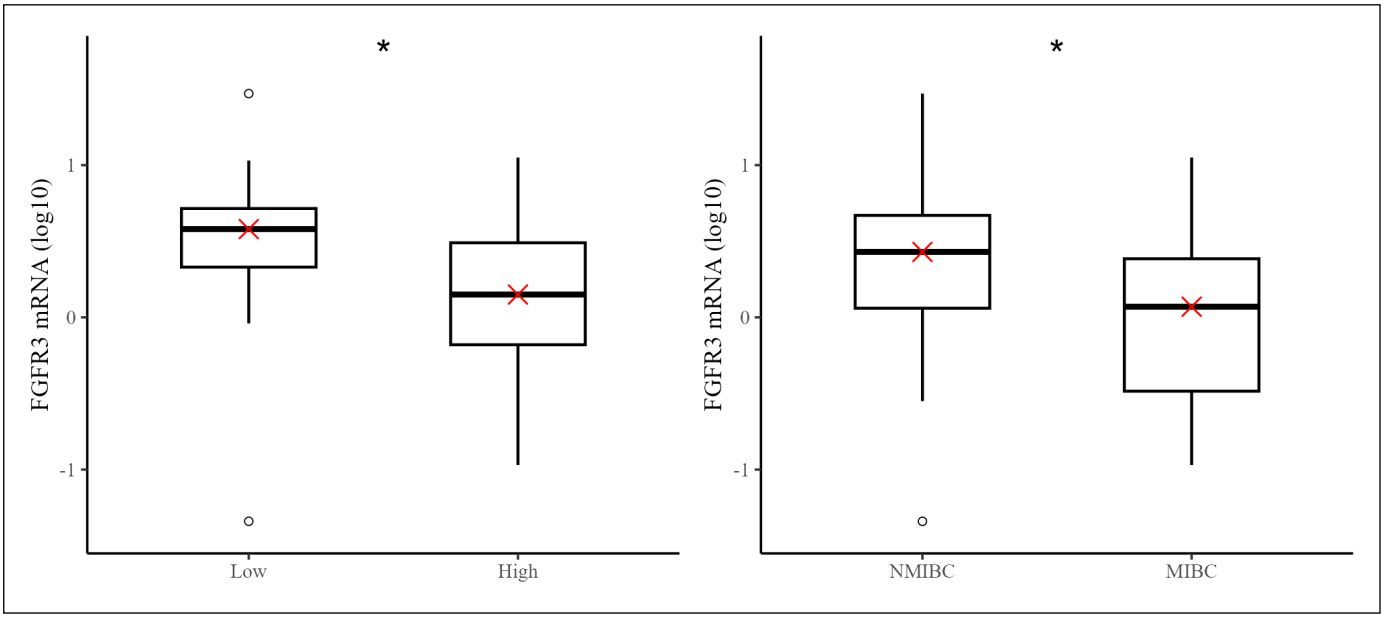


Figure 2. *Distribution of FGFR3 log_{10} mRNA expression by clinical phenotype. Left: grade (low vs high). Right: invasiveness (NMIBC vs. MIBC). Boxes represent the interquartile range with horizontal lines for medians and whiskers for 1.5 × IQR. Red cross = mean.*

**p <0.05 by Wilcoxon rank-sum test.*

sociated with overall survival in the whole cohort (HR = 0.52, 0.25–1.06; p = 0.072; Table 6; Figure 1).

Exploratory clinicopathological associations

In an exploratory model of tumor size (<3 cm vs ≥3 cm), higher *FGFR3* mRNA was associated with smaller tumors (OR 4.94, 95% CI: 1.63–15.01; p = 0.005; AUC 0.72; Brier 0.206; N = 80). Age showed no association. Full results are reported in Suppl. Table 2.

Additional exploratory analyses of *FGFR3* expression across clinicopathologic groups are provided in the Supplement Materials (Tables 2–4). Suppl. Table 2 shows higher *FGFR3* in low- vs high-grade, NMIBC vs MIBC, and <3 cm vs ≥3 cm tumors (all p <0.001), with no difference by focality (p = 0.820). Complementary logistic models using alternative *FGFR3* parameterizations (median split; quartiles) support these contrasts for invasiveness and grade (e.g., OR 5.65 for high-vs-low ≥ median predicting NMIBC; OR 10.99 for Q4 vs Q1 predicting low grade). These analyses were prespecified as exploratory; p-values were two-sided and not adjusted for multiplicity.

Table 3. *Logistic regression for tumor grade (low vs high) with FGFR3 log_{10} mRNA expression and age. Outcome coding: low grade = 1, high grade = 0. Predictors: FGFR3 (log_{10}) and age (years). Odds ratios (OR) >1 indicate higher odds of low grade. Two-sided Wald p-values*

Predictor	OR	95% CI	p-value
FGFR3 mRNA (log_{10})	5.99	1.78–20.13	0.004
Age (per year)	0.99	0.94–1.04	0.726

Table 4. *Discrimination (AUC) and calibration (Brier) for binary outcomes. Models: univariable logistic regression with FGFR3 mRNA (log_{10}) as the sole predictor. Positive-class coding: invasiveness – MIBC = 1; grade – high = 1. Metrics: AUC (95% CI; DeLong) and Brier score*

Outcome	AUC	Brier score
NMIBC vs MIBC	0.74	0.180
Low vs high grade	0.74	0.189

Table 5. *Cox proportional hazards model — recurrence-free survival (NMIBC). Outcome: recurrence-free survival (event = recurrence). Predictors: FGFR3 mRNA (log_{10}), age (years), and grade (high vs low). Hazard ratios (HR) >1 indicate an increased risk of recurrence. Two-sided Wald p-values; 95% confidence intervals in brackets. N = 54; events = 17*

Predictor	HR	95% CI	p value
FGFR3 mRNA (log_{10})	1.09	0.37–3.20	0.880
Age (per year)	1.03	0.98–1.09	0.191
High grade (vs low)	2.16	0.78–5.94	0.137

Table 6. *Cox proportional hazards model – overall survival (all patients). Outcome: overall survival; event = death. Predictors: FGFR3 mRNA (log_{10}), age (years), and grade (high vs low). Hazard ratios (HR) >1 indicate an increased risk of death. Two-sided Wald p-values*

Predictor	HR	95% CI	p value
FGFR3 mRNA (log_{10})	0.52	0.25–1.06	0.072
Age (per year)	1.07	1.02–1.12	0.003
High grade (vs low)	19.17	2.59–141.73	0.004

DISCUSSION

In this cohort of fresh-frozen bladder cancer tissues, tumor *FGFR3* mRNA expression was independently associated with a less aggressive phenotype, with greater odds of NMIBC compared with MIBC and of low-grade compared with high-grade disease. An association with smaller tumor size was also observed, although this finding should be viewed in the context of an exploratory analysis and may be influenced by subgroup imbalance.

While higher *FGFR3* mRNA expression was more frequently observed in NMIBC, the magnitude of the association warrants cautious interpretation. Variability across estimates likely reflects cohort size and group composition, indicating a consistent direction of effect but limited precision in its quantification.

Model discrimination was moderate for both phenotype outcomes (NMIBC vs MIBC and low-grade vs high-grade disease), consistent with the established biology of *FGFR3* pathway activation in papillary, low-grade tumors and luminal-papillary molecular neoplasms [5–7, 16].

These results emphasize the clinical utility of TURBT-derived mRNA transcription analysis for phenotypic characterization.

By contrast, *FGFR3* expression showed no prognostic association regarding the recurrence-free survival in NMIBC and only a non-significant trend towards lower mortality in the total cohort. In light of the limited number of outcome events, the survival analyses may not be adequately powered to detect modest differences and should therefore be interpreted in an exploratory context.

Mixed prognostic signals have been reported across cohorts, platforms, and analytical thresholds, where-

as *FGFR3* mutation status has more consistently tracked with favorable features and outcomes in early-stage disease. Possible explanations include limited sample size, early administrative cut-offs with relatively few events, and imperfect correspondence between expression and genotype, as *FGFR3* overexpression can occur in wild-type tumors [10–12].

Overall, these findings support a pragmatic role for *FGFR3* mRNA as a phenotypic adjunct rather than a standalone prognostic biomarker. In settings where genotyping is unavailable at TURBT, *FGFR3* mRNA expression may refine baseline risk assessment alongside established clinicopathological parameters such as stage, grade, tumor size, and multiplicity.

However, for treatment selection in advanced disease, genomic profiling remains essential given current targeted therapy approvals for susceptible *FGFR3* alterations. Future studies should integrate expression, mutation, and fusion status within molecular classification frameworks and evaluate whether incorporating *FGFR3* mRNA expression into validated risk models improves clinical decision-making [8, 16, 17].

CONCLUSIONS

FGFR3 mRNA expression was strongly associated with tumor phenotype but did not provide independent prognostic information for survival. While expression may support phenotypic assessment at diagnosis, genomic testing remains essential for treatment selection in advanced disease.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

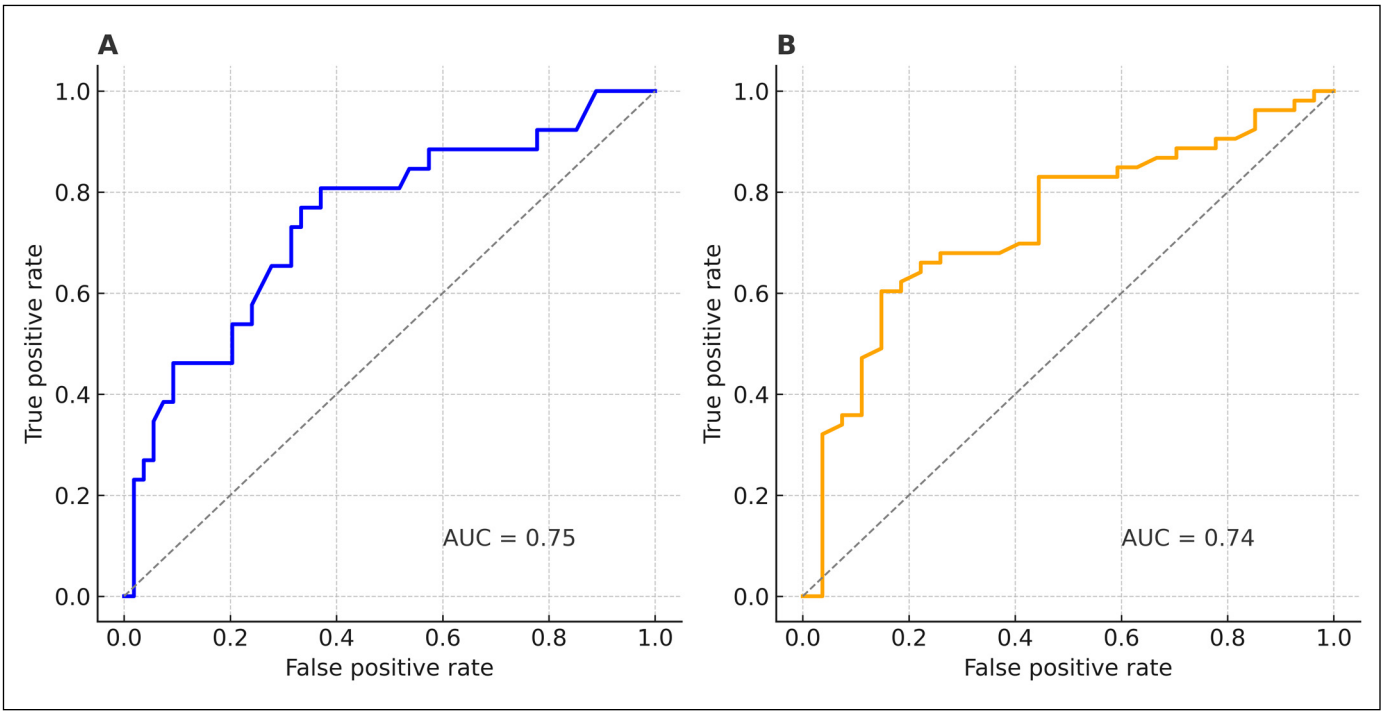
FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The study was approved by Ethics Committee of the University Clinic for Urology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje (IRB No. 03-16/2, January 4, 2021)

SUPPLEMENTARY MATERIALS



Suppl. Figure 1. *Receiver operating characteristic (ROC) curves for FGFR3 mRNA expression.* **A)** *Discrimination of non-muscle-invasive vs muscle-invasive bladder cancer (MIBC coded as positive outcome).* **B)** *Discrimination of low-grade vs high-grade tumors (high grade coded as positive outcome). The area under the curve (AUC) was 0.75 for invasiveness and 0.74 for grade. The diagonal dashed line represents the line of no discrimination.*

Suppl. Table 1. *Primer sequences and real-time PCR reaction conditions*

Primer sequences		
Gene	Primer	Sequence (5'→3')
FGFR3	Forward	CGTACTGTGCCACTTCAGTG
FGFR3	Reverse	CCAGCAGCTTCTTGTCCATC
GAPDH	Forward	TGCACCACCAACTGCTTAGC
GAPDH	Reverse	GGCATGGACTGTGGTCATGAG
Real-time PCR reaction conditions		
Step	**Temperature**	**Time**
Initial denaturation	95°C	10 min
Denaturation	95°C	15 s
Annealing	58°C	30 s
Extension	72°C	30 s
Number of cycles	–	40 cycles
Melt-curve analysis	58–95°C	Incremental increase of 0.3°C

Suppl. Table 2. *Logistic regression for tumor size (<3 cm vs ≥3 cm). Outcome coding: <3 cm = 1, ≥3 cm = 0. Predictor: FGFR3 mRNA (log_{10}). Odds ratios (OR) >1 indicate higher odds of <3 cm. Metrics: AUC (95% CI; DeLong) and Brier score. Two-sided Wald p-values*

Predictor	OR	95% CI	p value
FGFR3 mRNA (log_{10})	4.94	1.63–15.01	0.005
Age (per year)	0.99	0.94–1.05	0.816

Suppl. Table 3. *Distribution of FGFR3 log_{10} mRNA expression across clinical groups. Values are given as median (interquartile range)*

Variable	Group	n	*FGFR3* mRNA (log_{10}), median (IQR)	p value
Grade	LG HG	27 53	0.58 (0.33–0.71) 0.15 (–0.18–0.49)	<0.001
Invasiveness	NMIBC MIBC	54 26	0.45 (0.10–0.67) 0.03 (–0.51–0.24)	<0.001
Tumor size	<3 cm ≥3 cm	31 49	0.49 (0.26–0.70) 0.07 (–0.24–0.51)	<0.001
Focality	Unifocal Multifocal	60 20	0.28 (–0.07–0.67) 0.34 (0.05–0.54)	0.820

HG – high grade; LG – low grade; MIBC – muscle-invasive bladder cancer; NMIBC – non-muscle-invasive bladder cancer

Suppl. Table 4. *Alternative parameterizations of FGFR3 in logistic models. Outcomes/coding: (A, C) invasiveness – NMIBC = 1, MIBC = 0; (B, D) grade – low = 1, high = 0. Predictors: A/B use FGFR3 median split; C/D use FGFR3 quartiles (ref Q1 = lowest). All models adjusted for age. Results shown as OR (95% CI) and p value (two-sided)*

Predictor (category vs reference)	OR	95% CI	p-value
High (≥ median) vs low (<median)	5.65	1.94–16.42	0.001
B) Grade (low vs high) – FGFR3 median split (ref: Low)			
High (≥ median) vs low (< median)	6.24	2.15–18.15	<0.001
C) Invasiveness (NMIBC vs MIBC) – *FGFR3* quartiles (ref: Q1)			
Q2 vs Q1 (lowest)	2.26	0.64–8.00	0.208
Q3 vs Q1 (lowest)	8.48	1.85–38.79	0.006
Q4 (highest) vs Q1 (lowest)	8.49	1.86–38.79	0.006
D) Grade (low vs high) – *FGFR3* quartiles (ref: Q1)			
Q2 vs Q1 (lowest)	2.25	0.36–14.00	0.383
Q3 vs Q1 (lowest)	8.95	1.63–49.24	0.012
Q4 (highest) vs Q1 (lowest)	10.99	2.00–60.56	0.006

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