TURKISH JOURNAL OF UROLOGY
Turk J Urol 2020; 46(3): 206-12 • DOI: 10.5152/tud.2020.19186
UROONCOLOGY
Original Article

Role of serum and urine transforming growth factor beta 1, matrix metallopeptidase 9, tissue inhibitor of metalloproteinase 2, and nerve growth factor beta levels and serum neutrophil-to-lymphocyte ratio in predicting recurrence and progression risks in patients with primary non-muscle invasive bladder cancer

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Cite this article as: Efiloğlu Ö, İşbilen Başok B, Turan T, Toprak T, Erol B, Çaşkurlu T, et al. Role of serum and urine transforming growth factor beta 1, matrix metallopeptidase 9, tissue inhibitor of metalloproteinase 2, and nerve growth factor beta levels and serum neutrophil-to-lymphocyte ratio in predicting recurrence and progression risks in patients with primary non-muscle invasive bladder cancer. Turk J Urol 2020; 46(3): 206-12.

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Submitted:
18.09.2019

Accepted:
23.12.2019

Available Online Date:
07.02.2020

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ABSTRACT

Objective: The current study aimed to examine the correlation between serum and urine transforming growth factor beta 1 (TGF-β1), matrix metallopeptidase 9 (MMP-9), tissue inhibitor of metalloproteinase 2 (TIMP-2), and nerve growth factor beta (NGF-β) levels and serum neutrophil-to-lymphocyte ratio (NLR) as well as the recurrence and progression risks of non-muscle invasive bladder cancer (NMIBC).

Material and methods: The current study included 89 individuals: n=47, patients with primary NMIBC (patient group) and n=42, healthy controls (control group). The TGF-β1, MMP-9, TIMP-2, and NGF-β levels in the blood and urine samples were assessed using an enzyme-linked immunosorbent assay. Moreover, the serum NLR was evaluated. For the statistical analysis, a generalized linear model was used to compare the groups. In the analysis, gender and use of cigarettes were used as the secondary factors, and age was included as the covariate in the generalized linear model set for the intergroup evaluations. Meanwhile, a logistic regression model was utilized to evaluate the impact of the biomarkers on the risk of recurrence and progression.

Results: The serum NLR was higher in the patient group than in the control group (p=0.033). The patients with disease recurrence had higher body mass index and MMP-9 levels, but the results were not statistically significant. Moreover, the patients with a high NLR had a high risk of disease progression (odds ratio [OR]=13.046, 95% confidence interval [CI]=1.057–161.18, p=0.045), whereas the patients with a high serum TGF-β1 level (OR=0.972, 95% CI=0.945–0.999, p=0.047) had a low risk of disease progression.

Conclusion: High NLR and low TGF-β1 values were associated with an increased risk of disease progression in patients with NMIBC. However, no relationships were found between TGF-β1, MMP-9, TIMP-2, and NGF-β values and the recurrence of NMIBC.

Keywords: Bladder cancer; MMP-9; NGF-β; neutrophil-to-lymphocyte ratio; TGF-β1; TIMP-2.

Introduction

Non-muscular invasive bladder cancer (NMIBC) is a heterogeneous disease in terms of recurrence, progression, and mortality. The recurrence rate of NMIBC is approximately 50%–70%, and that of progression is about 10%–20%.[1] High-grade T1 tumors have the highest risk of recurrence and progression.[2] Molecular markers are promising diagnostic tools for the current screening methods for cancer; however, the biomarkers used in the diagnosis of low-level tumors have low sensitivity and specificity. Because prospective studies about the impact of tumor markers on recurrence and progression have not been conducted, the use of bladder tumor markers has not been widely accepted.[3]

Thus, the current study aimed to evaluate the relationships between transforming growth

factor beta 1 (TGF-β1), matrix metalloproteinase 9 (MMP-9), tissue inhibitor of metalloproteinase 2 (TIMP-2), and nerve growth factor beta (NGF-β) levels and serum neutrophil-to-lymphocyte ratio (NLR) as well as the recurrence and progression of primary NMIBC.

Material and methods

After the ethics committee approved the study (decision no: 2015/0050), blood and urine samples were collected from 47 patients diagnosed with primary bladder cancer and 42 healthy individuals (control group) between January 2014 and January 2015. However, patients with macroscopic hematuria, overactive bladder symptoms, active infections, and non-urogenital system malignancies were excluded from the study.

The MMP-9, NGF-β, TGF-β1, and TIMP-2 levels in the serum and urine samples of each participant were assessed. The urine MMP-9, NGF-β, TGF-β1, and TIMP-2 levels were provided in proportion to the creatinine levels in the spot urine assessment, and the results were expressed as pg/mg creatinine or ng/mg creatinine. In addition, in the venous blood samples obtained from the patient and control groups before the first transurethral resection (TUR), the neutrophil and lymphocyte values were divided by one another to determine the NLR. The demographic data of all patients, including body mass index (BMI) and smoking history, were recorded. Moreover, information about tumor stage (Ta, T1), grade (low, high grade), presence of carcinoma in situ (CIS), tumor size, number of patients with bladder cancer, and recurrence and progression statuses was obtained.

After the TUR, each patient received intravesical therapy, as indicated in the European Association of Urology guidelines for NMIBC. Moreover, in accordance with the recent guidelines, a follow-up schedule was planned based on the regular cystoscopy.[4] Recurrence was defined as the diagnosis of tumors during the cystoscopy follow-up sessions, and patients who presented with recurrence underwent TURs. Meanwhile, progression was defined as the progression of pathological state to an advanced level in terms of stage (from pTa to pT1 or from pTa, pT1, to pT2) or grade (from low to high grade) after the TURs.

Main Points:

- Lymphocytic response plays an important role in the control of cancer progression. Lymphocytopenia leads to a decreased cellular immune response. The decrease in T-cell activity within the tumor accelerates primary tumor progression.
- Transforming growth factor controls various cellular processes, such as cell proliferation, differentiation, and adhesion; extracellular matrix formation; and apoptosis.
- Matrix metalloproteinases are involved in metastasis, invasion, angiogenesis, apoptosis, and adhesion.
- TIMPs have different biological activities, such as participating in cell apoptosis and survival as well as cell growth promotion and inhibition.
- High NLR and low TGF-β1 values were correlated to an increased risk of disease progression in patients with NMIBC.

Statistical analysis

For the statistical analysis, the Number Cruncher Statistical System 2007 (NCSS Statistical Software, Kaysville, UT, the USA) was used. While evaluating the data obtained during the study, along with the definitive statistical methods (average, standard deviation, median, frequency, ratio, minimum, and maximum), the normality of the quantitative data was assessed using the Shapiro–Wilk's test and graphical examinations. An independent samples *t*-test was used to compare the quantitative variables with a normal distribution in both groups, and the Mann–Whitney U test was utilized to compare the quantitative variables without a normal distribution in both groups. The Pearson's chi-squared test and the Fisher's exact test were used to compare the qualitative data. Because the blood and urine samples did not have normal distributions, they were analyzed using the generalized linear model. To co-evaluate the impact of the risk factors on recurrence and progression, both were considered as dependent variables, and a binary logistic regression analysis was performed. A p value <0.05 was considered statistically significant.

Results

The demographic data of the patient and control groups are shown in Table 1. No statistical differences were found between the two groups in terms of age and BMI.

The two groups significantly differed in terms of gender distribution and use of cigarettes (p=0.001 and 0.007, respectively). Therefore, gender and use of cigarettes were considered as the secondary factors, and age was used as the covariate in the generalized linear model set for the intergroup evaluations. Table 2 shows the results of the comparison between the blood and urine samples of the patient and control groups. The NLR and urine NGF-β levels were high in the patient group (NRL: $\chi^2=10.445$, p=0.034; urine NGF-β level: $\chi^2=10.304$, p=0.036). The other variables were similar between the patient and control groups (Table 2) (p>0.05).

During approximately 27.5 months of follow-up, recurrence was observed in 19 patients and progression in five patients (n=4, stages and n=1, grade). The results of the univariate and multivariate analyses of the model that aimed to predict disease recurrence are summarized in Tables 3 and 4. In the univariate analysis, a relationship was found between number of tumors (p=0.036) and disease recurrence. In the multivariate analysis, although a relationship was observed between recurrence and

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Table 1. Distribution of descriptive properties

		Patient group (n=47)	Control group (n=42)	p
		Average±SD	Average±SD	
Age (years)		64.36±11.00	60.07±10.52	[a]0.064
BMI (kg/m^2)		26.82±4.13	26.37±2.62	[a]0.535
		n (%)	n (%)	
Sex	Female	7 (29.2)	17 (70.8)	[b]0.007**
	Male	40 (61.5)	25 (38.5)	
Smoking	No	6 (24.0)	19 (76.0)	[b]0.001**
	Yes	41 (64.1)	23 (35.9)	

[a]Independent t-test, [b]Pearson chi-squared test, **p<0.01, BMI: body mass index; SD: standard deviation

Table 2. Evaluation of biomarker levels in the urine and blood between the two groups

	Patient group (n=47)	Control group (n=42)	
	Mean±SD (median)	Mean±SD (median)	p
NLR	2.33±0.91 (2.19)	1.90±0.45 (1.86)	0.034[†]
Urine MMP-9 level (ng/mL)	40.58±72.83 (11.06)	17.76±19.95 (9.13)	0.077
Urine MMP-9 level (ng/mg)/Cr level	55.66±94.15 (13.67)	28.20±48.72 (13.89)	0.224
Urine NGF-β level (pg/mL)	47.70±47.09 (30.56)	39.43±44.56 (20.06)	0.694
Urine NGF-β level (pg/mg)/ Cr level	63.45±69.10 (35.60)	53.46±59.15 (29.19)	0.036[†]
Urine TGF-β1 level (ng/mL)	0.21±0.09 (0.19)	0.20±0.11 (0.17)	0.114
Urine TGF-β1 level (pg/mg)/Cr level	281.23±235.19 (203.24)	285.18±237.82 (209.72)	0.907
Urine TIMP-2 level (pg/mL)	5330.71±4552.62 (4799.32)	4722.54±3707.47 (4179.59)	0.430
Urine TIMP-2 level (pg/mg)/Cr level	5766.73±5536.00 (4612.96)	4746.86±2296.76 (4632.89)	0.277
Urine MMP-9/TIMP-2 ratio	25.45±102.42 (3.65)	10.54±31.16 (3.96)	0.224
Serum MMP-9 level (ng/mL)	1085.71±316.90 (1197.94)	1070.15±250.78 (1127.64)	0.657
Serum NGF-β level (pg/mL)	38.99±12.62 (41.10)	39.38±9.56 (40.20)	0.618
Serum TGF-β1 level (ng/mL)	0.47±0.12 (0.46)	0.48±0.13 (0.48)	0.849
Serum TIMP-2 level (ng/mL)	64.29±15.06 (61.77)	58.94±9.02 (58.48)	0.072
Serum MMP-9/TIMP-2 ratio	17.62±6.54 (18.21)	18.49±5.23 (18.82)	0.258

Generalized linear model. [‡]Analyses were performed after adjusting for age, gender, and smoking history. [†]The model for the relevant variable was statistically significant. p values represent the statistical significance of the group variables.
Cr: creatinine; NLR: neutrophil-to-lymphocyte ratio; MMP-9: matrix metallopeptidase 9; NGF-β: nerve growth factor beta; TGF-β1: transforming growth factor beta 1; TIMP-2: tissue inhibitor of metalloproteinase 2; SD: standard deviation

high serum MMP-9 level, the result was not statistically significant (p=0.056). The univariate and multivariate analyses of the factors affecting progression are summarized in Tables 3 and 5. In the univariate analysis, a high grade (p=0.022) and low serum TGF-β1 level (p=0.023) were correlated to disease progression (Table 3). In the multivariate analysis, a high NLR (odds ratio [OR]=13.046, 95% confidence interval [CI]=1.057–161.18, p=0.045] and low serum TGF-β1 level (OR=0.972, 95% CI=0.945–0.999, p=0.047) were associated with an increased risk of progression (Table 5).

Discussion

Extracellular matrix (ECM) elements play an important role in tumor invasion and metastasis. ECM is a multi-tasking entity that includes proteins and proteoglycans, and it provides structural support to organisms during processes, such as cell proliferation, differentiation, and migration. Moreover, it acts as a primary barrier to prevent tumor tissue growth and tumor cell proliferation. In the invasion and metastasis of cancer, the ECM must be broken down, which requires metalloproteinases. [5]

Table 3. Univariate analysis of the factors affecting relapse and progression

		Non-recurrent (n=28) (Mean±SD)	Recurrent (n=19) (Mean±SD)	p	Non-progressive (n=42) Mean±SD (median)	Progressive (n=5) Mean±SD (median)	p
Age (years)		64.60±11.14	64±11.08	0.855	63.64±10.67 (63.5)	70.4±13.24 (65)	0.336
BMI (kg/m²)		25.97±3.5	28.06±4.7	0.088	27.11±4.28 (25.77)	24.37±0.8 (24.22)	0.119
Number of tumor, n (%)		1.86±1.23	3.11±2.66	0.036	2.3±2.01	2.6±1.78	0.755
Tumor size, n (%)							
<3 cm		11 (39.3)	6 (31.6)	0.589	16 (94.1)	1 (5.9)	0.640
≥3 cm		17 (60.7)	13 (68.4)		26 (86.7)	4 (13.3)	
NLR		2.29±0.8	2.38±0.9	0.737	2.24±0.86 (2.18)	3.08±1.07 (3.56)	0.095
Urine MMP-9 level (ng/mL)		38.88±77.43	43.07±67.45	0.849	40.57±76.72 (10.05)	40.66±25.88 (45.4)	0.190
Urine MMP-9 level (ng/mg)/Cr level		61.20±112.5	47.98±59.3	0.630	56.25±98.92 (12.05)	50.72±40.24 (35.88)	0.119
Urine NGF-β level (pg/mL)		55.15±57.7	36.71±21.42	0.191	49.17±48.95 (31.3)	35.33±26.97 (29.12)	0.512
Urine NGF-β level (pg/mL)/Cr level		76.37±84.21	44.40±30.38	0.121	64.78±71.74 (36.57)	52.23±44.64 (29.85)	0.907
Urine TGF-β1 level (ng/mL)		0.20±0.08	0.22±0.08	0.349	0.21±0.08 (0.2)	0.24±0.16 (0.17)	0.960
Urine TGF-β 1 level (pg/mg)/Cr level		288±277.6	271.1±159.8	0.812	275.24±235.8 (202.53)	331.53±250.32 (286.29)	0.470
Urine TIMP-2 level (pg/mL)		4738±2907	6204±6239	0.283	4767.11±3043.17 (4644.45)	10065.03±10586.62 (5134.3)	0.627
Urine TIMP-2 level (pg/mg)/Cr level		5439±5969	6248±4944	0.628	5302.02±5130.92 (4570.52)	9670.29±7828.43 (4689.79)	0.271
Urine MMP-9/ TIMP-2 ratio		35.69±132.3	10.33±12.07	0.411	27.29±108.27 (3.71)	9.92±11.77 (3.16)	0.933
Serum MMP-9 level (ng/mL)		1016±360	1187±207	0.070	1082.98±334.07 (1197.94)	1108.66±101.09 (1086.16)	0.700
Serum TGF-β1 level (ng/mL)		0.47±0.12	0.47±0.11	0.954	0.49±0.11 (0.47)	0.36±0.09 (0.35)	0.023*
Serum NGF-β level (pg/mL)		38.92±11.08	39.07±14.92	0.969	39.58±12.45 (44.05)	34.04±14.43 (34.1)	0.336
Serum TIMP-2 level (ng/mL)		62.19±12.95	67.38±17.63	0.250	63.23±11.67 (61.51)	73.25±33.15 (62.15)	0.776
Serum MMP-9/TIMP-2 ratio		16.98±7.31	18.55±5.22	0.423	17.61±6.49 (18.33)	17.65±7.77 (15.62)	0.933
Tumor grade (%), n (%)	Low	20	11	0.337	30 (96.8)	1 (3.2)	0.022
	High	8	8	12 (75.0)	4 (25.0)		
Tumor stage, n (%)	Ta	10	6	0.769	15 (93.8)	1 (6.3)	0.483
	T1	18	13		27 (87.1)	4 (12.9)	
CIS, n (%)	+	3	3	0.609	5 (83.3)	1 (16.7)	0.608
	-	25	16		37 (90.2)	4 (9.8)	

BMI: body mass index; CIS: carcinoma in situ; Cr: creatinine; SD: standard deviation; NLR: neutrophil-to-lymphocyte ratio; MMP-9: matrix metallopeptidase 9; NGF-β: nerve growth factor beta; TGF-β1: transforming growth factor beta 1; TIMP-2: tissue inhibitor of metalloproteinase 2

Matrix metalloproteinases are a family of calcium-dependent zinc-containing endopeptidases responsible for tissue remodeling and degradation of ECM proteins. They are involved in metastasis, invasion, angiogenesis, apoptosis, and adhesion.[6]

Tissue inhibitors of metalloproteinase (TIMPs) are major inhibitors of MMPs. TIMPs have different biological activities, such as participating in cell apoptosis and survival as well as cell growth promotion and inhibition.[7]

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Table 4. Logistic regression analysis of the factors affecting recurrence

	HR	95% CI	p
BMI	1.176	0.984–1.405	0.075
Number of tumors	1.378	0.943–2.013	0.098
Urine NGF-β level/Cr level	0.994	0.982–1.005	0.279
		1.000–1.005	
Serum MMP-9 level	1.002		0.056
Constant	0.001		0.016

BMI: body mass index; NGF-β: nerve growth factor beta: Cr: creatinine; MMP-9: matrix metallopeptidase 9; HR: hazard ratio; 95% CI: 95% confidence interval

Table 5. Logistic regression analysis of the factors affecting progression

	HR	95% CI	p
NLR	13.046	1.057–161.018	0.045*
Serum TGF-β1 level	0.972		0.047*
Constant	16.345	0.945–0.999	0.396

BMI: body mass index; NGF-β: nerve growth factor beta: Cr: creatinine; MMP-9: matrix metallopeptidase 9; HR: hazard ratio; 95% CI: 95% confidence interval

In the study of Fernandez et al.[8], the MMP-9 levels were higher in patients with NMIBC than in healthy controls based on a urine MMP-9 analysis using an enzyme-linked immunosorbent assay. In the patient group, the cut-off value for the MMP-9 level was 0.819 ng/mL, with a sensitivity of 80% and specificity of 71%. In our study, although the MMP-9 level was higher in the patient group than in the control group, a cut-off value with high sensitivity and specificity could not be identified due to the small number of patients. In the study of Angulo et al.[9], the MMP-9 levels in the peripheral blood of patients with bladder cancer were higher than those of healthy controls based on a real-time polymerase chain reaction. However, the TIMP-2 levels did not differ. Moreover, the MMP-9 levels were higher in patients with bladder cancer with a higher grade or stage. However, no relationships were found between the TIMP-2 levels and the grade and stage of the disease. Gohji et al.[10] have shown no significant differences in the serum MMP-2 and TIMP-2 levels between patients with NMIBC and healthy controls. However, a significant difference in the serum MMP-2 and TIMP-2 levels was noted in patients with muscle invasive cancer. Although the serum TIMP-2 level was high in patients with muscle invasive bladder cancer, it did not significantly differ to that of patients with NMIBC. Our study showed that the TIMP-2 level in the urine and serum was not correlated to disease recurrence and progression. However, Hara et al.[11] have observed that the MMP-9 and TIMP-2 mRNA expressions were 2.5 and 3 times higher, respectively, in NMIBC patients with recurrence. In our study, the MMP-9 level was high in patients with recurrence, and the result was almost statistically significant (p=0.056).

Transforming growth factor controls various cellular processes, such as cell proliferation, differentiation, and adhesion; extracellular matrix formation; and apoptosis. TGF mediates epithelial-mesenchymal transition, invasion, and metastasis. TGF beta is activated by calpain, cathepsin D, chymase, elastase, kallikrein, MMP-9, neuraminidase, plasmin and thrombospondin-1, and endoglycosidase F.[12]

Transforming growth factor can act as both tumor suppressor and oncogene in cancer development. Hyperplasia develops when there is an interruption in the TGF pathway. In premalignant conditions, the cells proliferate uncontrollably as a result of suppression of the TGF pathway, thereby leading to the development of cancer. The tumor suppressive effect of TGF is prevented via proliferation in tumor cells.[13]

Some studies have found that benign urothelial and low-grade tumors have higher TGF-β1 expressions than CIS and high-grade tumors.[14] In a study of patients with bladder cancer conducted by Baharlou et al.[15], the serum interleukin-17 and TGF-β1 levels in early-stage tumor, low-grade tumor, and non-metastatic patients were lower than those of the controls. However, no significant differences were found in terms of tumor stage, grade, size, metastasis, and invasion. TGF-β1 is released by regulatory T cells and tumors in the late stages of solid cancer. In a previous study, a decrease in serum TGF-β1 level and chemotherapy were found to suppress tumor progression and regulatory T cells. In another study, in the immunohistochemical evaluation of pathologies in 80 patients with invasive bladder tumors who underwent radical cystectomies, a correlation was found between the overexpression of TGF-β1 and progression of bladder cancer.[16] Shariat et al.[17] have found that an increase in plasma TGF-ß1 level before cystectomy in patients with muscle invasive bladder cancer is correlated to bladder cancer aggression, recurrence rate, and cancer-specific survival. In our study, the serum and urine TGF-β1 values were not correlated to recurrence. However, a decrease in the serum TGF-β1 value was associated with progression (OR=0.972, 95% CI=0.945–0.999, p=0.047).

Nerve growth factor is the first member of the neurotrophin family that was discovered. Neurotrophins are from the growth factor family of polypeptides that affect the survival and function of neurons and control synaptic function and plasticity. NGF is required for the development of neurons in the peripheral nervous system and functional integrity of cholinergic neurons in the central nervous system. Moreover, it acts biologically via a typical tyrosine kinase receptor (tropomyosin kinase receptor A) and binds to a neurotrophin receptor (p75 NTR) to a lesser extent.[18]

Studies have shown a correlation between NGF-β level and malignancy.[19,20] However, no study in the literature has found an association between NGF-β level and NMIBC. Our study revealed that the NGF-β values of the patient and control groups were similar in the generalized linear model. Moreover, the NGF-β values had no contributions in predicting the recurrence and progression risks in patients with NMIBC.

According to the most recent theories, the systemic inflammatory response triggered by cancer causes relative neutrophilia and lymphocytopenia. Growth and proangiogenic factors, which are anti-apoptotic markers required for tumor growth and progression, increase the number of neutrophils. Lymphocytic response plays an important role in the control of cancer progression. Lymphocytopenia leads to a decreased cellular immune response. The decrease in T-cell activity within the tumor accelerates primary tumor progression.[21] In this study, the NLR was higher (p=0.033) in the patient group than in the control group. Moreover, in the model set for progression, a high NLR increased the risk of progression (p=0.045). Similar to our study, Mano et al.[22] have found that the NLR estimation points for recurrence and progression were 2.43 and 2.41, respectively, in 122 patients with NMIBC. According to the study, a positive correlation was observed between a high tumor grade and NLR. Ceylan et al.[23] have reported a 50% probability of progression of Ta–T1 tumors in individuals with high NLRs. In the study conducted by Ozyalvacli et al.[21], the presence of more than one tumor and an NLR ≥2.43 were considered the risk factors for recurrence in patients with a bladder tumor larger than 3 cm. However, no relationship was found between NLR and disease progression. In our study, based on the assessment of the correlation between the number of tumors and disease recurrence, no relationship was found between NLR and disease recurrence. In a study of 1,551 patients with NMIBC, Kang et al.[24] have found that an NLR ≥2.0 is associated with poor overall survival and cancer-specific survival outcomes. However, some publications do not support these findings. Demirtas et al.[25] have conducted a study on 201 patients with invasive and intravesical treatment-resistant non-muscle invasive disease who underwent radical cystectomy. Results showed no significant difference in overall survival in patients with an NLR >2.5.

No relationships were found between TGF-β1, MMP-9, TIMP-2, and NGF-β levels and the recurrence of muscle invasive bladder cancer. However, this study revealed that a high NLR and low TGF-β1 level in patients with tumor progression could increase the risk of disease progression. The current study had fundamental limitations, which include the limited number of patients and short follow-up period. Overall, NMIBC is heterogeneous in terms of recurrence and progression. To determine the actual disease recurrence and progression, long-term follow-up is required.

In conclusion, high NLR and low TGF-β1 values were correlated to an increased risk of disease progression in patients with NMIBC. However, no relationships were found between TGF-β1, MMP-9, TIMP-2, and NGF-β levels and the recurrence of NMIBC.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul Medeniyet University (approval no: 2015/0050).

Informed Consent: Verbal informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.Y., T.Ç., Ö.E.; Design – T. Turan, Ö.E.; Supervision – B.E., T.Ç., A.Y.; Resources – T. Toprak; Materials – Ö.E.; Data Collection and/or Processing – Ö.E., T.T.; Analysis and/or Interpretation – B.İ.B., Ö.E., T. Turan; Literature Search – Ö.E., T. Turan; Writing Manuscript – Ö.E., T. Turan, T.Ç., A.Y.; Critical Review – A.Y., B.E., T.Ç.

Acknowledgements: This research was supported by the Scientific Research Unit of Istanbul Medeniyet University.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study was funded by the Scientific Research Unit of Istanbul Medeniyet University (Project No: T-UZM-2016-760).

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