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Clinical comparison of hematuria degree and pathology according to the AUA bladder cancer risk classification

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ABSTRACT

Aim: To determine the relationship between microhematuria level and bladder cancer diagnosis and staging.

Methods: A total of 452 patients who visited the Urology Clinic of the Faculty of Medicine of Afyonkarahisar Health Sciences University between 2017 and 2024 with complaints such as hematuria, dysuria, and suprapubic pain, and who underwent TUR-M surgery due to suspected bladder cancer-based on laboratory and imaging methods, were included. The pathology results confirmed the diagnosis of bladder cancer. In addition to demographic information such as age, gender, number of cigarettes smoked, and the presence of other risk factors for urothelial carcinoma (UC), data on hematuria levels, tumor stage and grade, American Urological Association (AUA) risk classification, microhematuria risk stratification, and pathological findings including lymphovascular invasion (LVI) and perineural invasion (PNI) were also recorded.

Results: Patients with more than 25 erythrocytes per microliter of urine or those with macroscopic hematuria had higher rates (42.1%) of additional risk factors for UC than other groups (p=0.040). The rate of high-stage and high-grade tumors was significantly higher in the group with >25 erythrocytes per microliter of urine compared to the other groups ($p < 0.001$, $p < 0.001$). When analyzing the AUA risk classification across the groups, 42 (32.8%) patients in the 3-10 erythrocyte group and 21 (35%) patients in the 10-25 erythrocyte group were classified as high risk. In contrast, 152 (64.7%) patients in the >25 erythrocyte group were classified as high risk, a rate significantly higher than in the other groups ($p < 0.001$).

Conclusions: Hematuria level is associated with tumor grade, tumor stage, and muscle invasion in bladder cancer. Given this association, it is crucial to carefully assess hematuria levels and the microhematuria risk classifications of patients.

Keywords: Hematuria, bladder cancer, urınary bladder neoplasms, AUA risk classification.

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1. Introduction

Hematuria, characterized by abnormal blood in the urine, is a common symptom encountered in urologic evaluations. It accounts for more than 20% of all such evaluations, highlighting its clinical significance. Hematuria occurs in two main forms: macroscopic and microscopic. Macroscopic hematuria refers to the presence of visible blood in the urine, whereas microhematuria is defined by the presence of ≥3 red blood cells in each large magnification area when examined under a microscope even if the appearance of the urine is normal [1].

The primary goal of hematuria evaluation is to identify or rule out any underlying malignancy. Hematuria plays a critical role in diagnosing serious pathologies, such as bladder cancer.

Bladder cancer is one of the leading causes of cancer-related deaths globally and it has a profound impact on patient quality of life, as well as significant implications for morbidity, mortality, and healthcare costs [2].

The majority of bladder cancer patients may initially present with macroscopic hematuria. However, hematuria is not always evident. In this case, the presence of microscopic hematuria may help make the diagnosis. That said, only about 2-5% of individuals with microhematuria are found to have a bladder tumor [3]. Indeed, review studies have reported microhematuria rates ranging from 2.4% to 31.1% among healthy volunteers, depending on the specific population studied [4].

In addition to urologic causes, nephrological and gynecologic conditions should also be taken into account in the differential diagnosis of microhematuria. For patients with microhematuria, clinicians should conduct a thorough history and physical examination to evaluate risk factors for genitourinary malignancies, medical kidney diseases, gynecologic conditions, and non-malignant causes of genitourinary microhematuria.

The detection of an underlying genitourinary malignancy in patients with microhematuria is strongly influenced by various risk factors. As a result, it is essential to conduct a detailed assessment of the patient's history [5].

The most common risk factors for urinary tract malignancy include male gender, age over 35 years, current or past smoking history, exposure to chemicals or dyes (such as benzenes and aromatic amines), and chronic use of analgesics. Additional risk factors include a history of macroscopic hematuria, urologic disease, irritative voiding symptoms, pelvic radiation, chronic urinary tract infections, exposure to known carcinogens like alkylating agents or chemotherapy, and prolonged foreign body exposure [6].

Numerous studies have documented low compliance with recommended diagnostic tests in patients with microhematuria, especially among women. The potential consequences of delayed or incomplete evaluation include a delayed diagnosis of malignancy. Notably, a higher proportion of women with bladder cancer die from the disease and its complications, which may be attributed to delayed diagnosis. Therefore, timely and thorough evaluation of patients with microhematuria represents a crucial opportunity for early detection of the disease [7].

Many patients with microscopic hematuria have no identifiable cause or pathology. However, a formal evaluation is essential, as malignancies are found in up to 2-5% of patients with microscopic hematuria and 30% to 40% of those with macroscopic hematuria [8].

Given that the likelihood of detecting malignancy in patients with microhematuria is relatively low, it is important to carefully weigh the benefits and potential risks of diagnostic evaluation at both the patient and healthcare system levels. Throughout the diagnostic process, clinicians should adopt a coordinated, multidisciplinary approach to ensure early detection of malignancy and provide optimal treatment.

In this regard, the American Urological Association (AUA), in collaboration with the Association for Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction, has developed a risk-based guideline that classifies patients into low, intermediate, and high-risk categories for urologic malignancy.

In low-risk patients with microhematuria, clinicians should engage in shared decision-

making with the patient to determine whether to repeat urinalysis in six months or proceed with cystoscopy and renal ultrasound. For patients classified as intermediate risk, both cystoscopy and renal ultrasound should be performed. In patients at high risk for malignancy, axial imaging of the upper urinary tract should be conducted in addition to cystoscopy [3].

The aim of this study was to use the AUA Microscopic hematuria stratification system and to verify the relationship between the level of microscopic hematuria according to this stratification system and the stage of the disease at the time of diagnosis and to verify whether demographic data such as age, smoking history, gender affect the level of microhematuria and pathology classification. In addition, although microhematuria is known to be a risk factor for bladder cancer, the relationship between microhematuria and bladder cancer stage and grade has not been specifically investigated. In our study, we aimed to investigate this relationship as well.

2. Materials and methods

The study was conducted at the Urology Clinic of Afyonkarahisar University of Health Sciences Hospital. Following ethical approval from the Clinical Research Ethics Committee of Afyonkarahisar University of Health Sciences (2011-KAEK-2, 2024/511), the data were collected retrospectively. The study was carried out in accordance with the principles of the Helsinki Declaration.

A total of 452 patients who visited the Urology Clinic of the Faculty of Medicine of Afyonkarahisar Health Sciences University between 2017 and 2024 with complaints such as hematuria, dysuria, and suprapubic pain, and who underwent TUR-M surgery due to suspected bladder cancer-based on laboratory and imaging methods, were included. The pathology results confirmed the diagnosis of bladder cancer. Since variant histology shows different clinical presentation and prognosis in bladder cancer, 11 patients with variant histology were excluded from the study. Due to the importance of smoking history in risk stratification of smoking, 15 patients whose smoking history was not recorded were excluded from the study. Patients in whom microscopic hematuria was not detected were excluded from the study because the risk level could not be determined. Patients who underwent investigations or cystoscopy for suspected bladder cancer but did not have the procedure at our center were excluded from the study. Consequently, the study proceeded with a total of 426 patients.

In addition to demographic information such as age, gender, number of cigarettes smoked, and the presence of other risk factors for urothelial carcinoma (UC), data on hematuria levels, tumor stage and grade, American Urological Association (AUA) risk classification, microhematuria risk stratification, and pathological findings including lymphovascular invasion (LVI) and perineural invasion (PNI) were also recorded. Hematuria levels were classified into three groups based on the AUA microhematuria risk stratification system: 3-10 erythrocytes per urine analysis, 10-25 erythrocytes, and more than 25 erythrocytes or macroscopic hematuria. According to the same system, cigarette consumption was categorized into three groups: less than 10 pack-years, 10-30 pack-years, and more than 30 pack-years(3). The tumor stage was classified as Ta, T1, and T2, while tumor grade was classified as either low grade or high grade.

In the first part of the study, data were analyzed across the three groups based on hematuria levels, and the relationship between hematuria levels and other demographic, clinical, and pathological variables was examined. In the

second part, the distribution of other variables was compared among the three smoking groups. The correlation of demographic, clinical, and pathological data for all patients in the study was analyzed without grouping. Factors potentially influencing muscle invasion were examined by comparing patients with muscle invasion (T2) to those without (Ta, T1).

2.1. Statistical Analysis: Statistical analysis of the data was performed with the IBM SPSS (Statistical Package for the Social Sciences) version 20.0 program. Whether the data had normal distribution was evaluated with the Kolmogorov-Smirnov test, histogram and Skewness-Kurtosis coefficients. For comparing paired groups, the Student's T-test was used for normally distributed variables, while the Mann-Whitney U test was used for parameters that did not have a normal distribution. Multivariate cross-tabulations were assessed using either the Chi-square test or the Fisher Exact test. The relationships between demographic, clinical, and pathological parameters were analyzed using Spearman's correlation test and Pearson's correlation test, as appropriate. In multivariate analysis, independent predictors of the muscle invasion outcome were examined with the enter method and Binary logistic regression analysis using possible factors identified in previous analyses. The Hosmer-Lemeshow test was used to assess model fit. Results were considered statistically significant when $p<0.05$.

3. Results

The study involved 426 patients diagnosed with bladder cancer who underwent TUR-M surgery. The mean age of the participants was 66.66 ± 11.54 years, with 377 (88.5%) being male. The relationship between the level of hematuria and clinical and pathological data is presented in Table 1. When the patients were categorized into three groups based on the severity of hematuria detected in their urine, no statistically significant differences were found between the groups in terms of age, gender, LVI, and PNI ($p = 0.075$, $p = 0.557$, $p = 0.966$, $p = 0.259$, respectively). Patients who smoked fewer than 10 pack-years or never smoked tended to have a lower grade of hematuria (60.3%), while those with a smoking history of more than 30 pack-years had a higher grade of hematuria (62.1%) ($p < 0.001$). Patients with more than 25 erythrocytes per microliter of urine or those with macroscopic hematuria had higher rates (42.1%) of additional risk factors for UC than other groups ($p=0.040$). The rate of high-stage and high-grade tumors was significantly higher in the group with >25 erythrocytes per microliter of urine compared to the other groups ($p < 0.001$, $p < 0.001$) (Figure 1, Figure 2). When analyzing the AUA risk classification across the groups, 42 (32.8%) patients in the 3-10 erythrocyte group and 21 (35%) patients in the 10-25 erythrocyte group were classified as high risk. In contrast, 152 (64.7%) patients in the >25 erythrocyte group were classified as high risk, a rate significantly higher than in the other groups ($p < 0.001$). In terms of microhematuria risk stratification, only 5 (3.8%) patients in the 3-10 erythrocyte group were classified as low risk, while the rest of the patients were categorized as either medium or high risk.

When patients were categorized into three groups based on their smoking history, those who smoked more than 30 pack-years were older than the other groups ($p < 0.001$). Among patients who smoked fewer than 10 pack-years, 37 (23.6%) were female, a significantly higher proportion compared to the other groups ($p < 0.001$). In the >30 pack-year smoking group, higher levels of hematuria, a greater number of additional risk factors for UC, and more advanced tumor stage and grade were observed compared to the other groups ($p < 0.001$ for all).

Table 1. The relationship between the hematuria level and clinical and pathologic data.

Parameters	3-10 Erythrocytes N=131 N (%)	10-25 Erythrocytes N=60 N (%)	>25 Erythrocytes N=235 N (%)	*p*
Age (Mean±SD)	64.83±11.52	66.60±13.25	67.69±11.00	*0.075**
Gender				
Male	115 (87.8)	51 (85)	211 (89.8)	*0.557*
Female	16 (12.2)	9 (15)	24 (10.2)	
Smoking status				
<10 pack-years or never smoked	79 (60.3)	22 (36.7)	56 (23.8)	
10-30 pack-years	26 (34.7)	16 (26.7)	33 (14)	***<0.001***
>30 pack-years	26 (34.7)	22 (36.7)	146 (62.1)	
Presence of Additional Risk Factors for UC				
Yes	41 (31.3)	17 (28.3)	99 (42.1)	***0.040***
No	90 (68.7)	43 (71.7)	136 (57.9)	
Tumor stage				
Ta	84 (64.1)	34 (56.7)	71 (30.2)	
T1	28 (21.4)	16 (26.7)	91 (38.7)	***<0.001***
T2	19 (14.5)	10 (16.7)	73 (31.1)	
Tumor grade				
Low grade	77 (58.8)	32 (53.3)	72 (30.6)	***<0.001***
High grade	54 (41.2)	28 (46.7)	163 (69.4)	
AUA risk classification				
Low risk	75 (57.3)	27 (45)	59 (25.1)	
Intermediate risk	13 (9.9)	12 (20)	24 (10.2)	***<0.001***
High risk	43 (32.8)	21 (35)	152 (64.7)	
Microhematuria risk stratification				
Low	5 (3.8)	0 (0)	0 (0)	
Middle	38 (29)	13 (21.7)	0 (0)	***<0.001***
High	88 (67.2)	47 (78.3)	235 (100)	
LVI				
Yes	17 (13)	7 (11.7)	29 (12.3)	*0.966*
No	114 (87)	53 (88.3)	206 (87.7)	
PNI				
Yes	9 (6.9)	5 (8.3)	9 (3.8)	*0.259*
No	122 (93.1)	55 (91.7)	226 (96.2)	

**: ANOVA test, Mean±SD: Mean±Standard Deviation, UC: Urothelial Carcinoma, LVI: Lymphovascular Invasion, PNI: Perineural Invasion, AUA: American Urological Association*

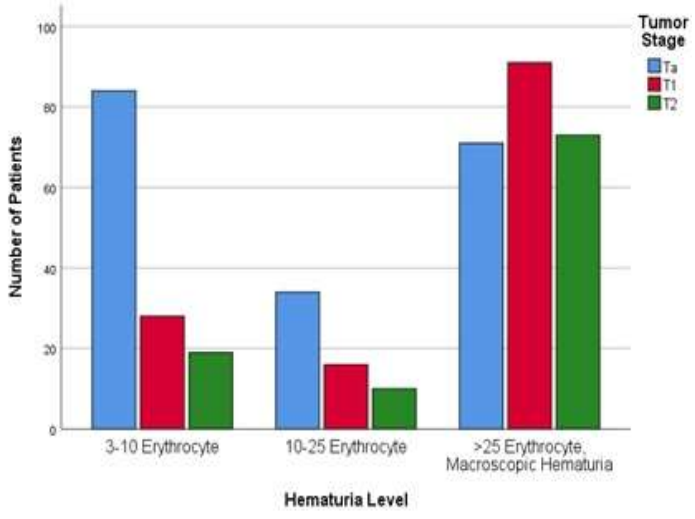

Figure 1. Tumor stages according to hematuria level.

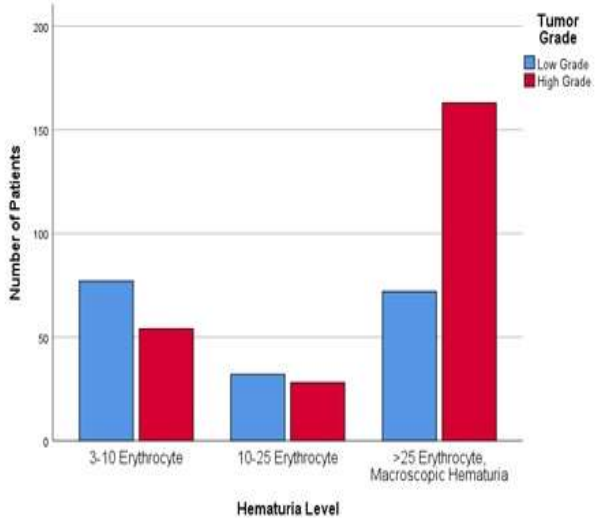

Figure 2. Tumor grades according to hematuria level

Additionally, 123 (63.4%) patients in this group were classified as high risk according to the AUA risk classification, which was significantly higher than in the other groups ($p < 0.001$). The presence of LVI and PNI detected on pathological examination was similar across all groups ($p = 0.096$, $p = 0.118$, respectively) (Table 2).

The correlation analysis of demographic, clinical, and pathological data revealed a weak to moderate positive correlation between the amount of smoking and the level of hematuria, which was statistically significant ($r = 0.390$, $p < 0.001$). Additionally, there was a weak positive and statistically significant correlation between

Table 2. Relationship between smoking status and clinical and pathologic data.

Parameters	**<10 Package-years N=157 N (%)**	**10-30 pack-years N=75 N (%)**	**>30 pack-years N=194 N (%)**	***p***
Age (Mean±SD)	64.20±13.63	62.11±10.83	70.41±8.77	*<0.001**
Gender				
Male	120 (76.4)	73 (97.3)	184 (94.8)	*<0.001*
Female	37 (23.6)	2 (2.7)	10 (5.2)	
Hematuria level				
3-10 erythrocytes	79 (50,3)	26 (34.7)	26 (13.4)	*<0.001*
10-25 erythrocytes	22 (14)	16 (21.3)	22 (11.3)	
>25 erythrocytes, macroscopic hematuria	56 (35.7)	33 (44)	146 (75.3)	
Presence of Additional Risk Factors for UC				
Yes	106 (67.5)	63 (84)	100 (51.5)	*<0.001*
No	51 (32.5)	12 (16)	94 (48.5)	
Tumor stage				
Ta	85 (54.1)	40 (53.3)	64 (33)	
T1	39 (24.8)	26 (34.7)	70 (36.1)	*<0.001*
T2	33 (21)	9 (12)	60 (30.9)	
Tumor grade				
Low grade	82 (52.2)	41 (54.7)	58 (29.9)	*<0.001*
High grade	75 (47.8)	34 (45.3)	136 (70.1)	
AUA risk classification				
Low risk	75 (47.8)	37 (49.3)	49 (25.3)	
Intermediate risk	18 (11.5)	9 (12)	22 (11.3)	*<0.001*
High risk	64 (40.8)	29 (38.7)	123 (63.4)	
Microhematuria risk stratification				
Low	5 (3.2)	0 (0)	0 (0)	
Middle	37 (23.6)	14 (18.7)	0 (0)	*<0.001*
High	115 (73.2)	61 (81.3)	194 (100)	
LVI				
Yes	24 (15.3)	4 (5.3)	25 (12.9)	*0.096*
No	133 (84.7)	71 (94.7)	169 (87.1)	
PNI				
Yes	13 (8.3)	2 (2.7)	8 (4.1)	*0.118*
No	144 (91.7)	73 (97.3)	186 (95.9)	

**: ANOVA test, Post-Hoc Tamhane's T2 analysis: (>30 pack-years) > (10-30 pack-years) (p>0.001), (>30 pack-years) > (<10 pack-years) (p<0.001), Mean±SD: Mean±Standard Deviation, UC: Urothelial Carcinoma, LVI: Lymphovascular Invasion, PNI: Perineural Invasion, AUA: American Urological Association*

Table 3. Correlation analysis of demographic, clinical and pathological data.

		Age (years)	G	S	HL	Presence of Additional Risk Factors for UC	TS	TG	LVI	PNI	AUA risk classification	Micro-hematuria risk stratification
Age (years)	r											
	p											
Gender	r	0.013										
	p	0.790										
Smoking	r	0.224	-0.250									
	p	**<0.001**	**<0.001**									
Hematuria level	r	0.104	-0.036	0.390								
	p	**0.032**	0.461	**<0.001**								
Presence of Additional Risk Factors for UC	r	0.283	-0.001	0.164	0.112							
	p	**<0.001**	0.985	**0.001**	**0.021**							
Tumor stage	r	0.191	-0.001	0.190	0.303	0.133						
	p	**<0.001**	0.989	**<0.001**	**<0.001**	**0.006**						
Tumor grade	r	0.173	-0.062	0.212	0.265	0.155	0.750					
	p	**<0.001**	0.200	**<0.001**	**<0.001**	**0.001**	**<0.001**					
LVI	r	-0.110	0.002	0.025	0.007	-0.110	-0.450	-0.310				
	p	**0.023**	0.965	0.604	0.892	**0.023**	**<0.001**	**<0.001**				
PNI	r	0.012	-0.012	0.079	0.069	0.010	-0.316	-0.205	0.602			
	p	0.806	0.812	0.105	0.157	0.833	**<0.001**	**<0.001**	**<0.001**			
AUA risk classification	r	0.194	-0.025	0.226	0.318	0.145	0.888	0.922	-0.326	-0.204		
	p	**<0.001**	0.611	**<0.001**	**<0.001**	**0.003**	**<0.001**	**<0.001**	**<0.001**	**<0.001**		
Micro-hematuria risk stratification	r	0.532	-0.030	0.357	0.406	0.213	0.284	0.240	-0.112	-0.067	0.295	
	p	**<0.001**	0.540	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.021**	0.166	**<0.001**	

r: correlation coefficient, UC: Urothelial Carcinoma, LVI: Lymphovascular Invasion, PNI: Perineural Invasion, AUA: American Urological Association), G: Gender, S: Smoking, HL: Hematuria level, TS: Tumor stage, TG: Tumor grade.

Table 4. Logistic regression analysis of factors affecting muscle invasion in bladder tumor.

Risk Factor	Muscle Invasion	
	RR (95% CI)	***p value***
Age (years)	1.022 (0.996-1.049)	*0.095*
Gender	1.080 (0.507-2.298)	*0.843*
Smoking	1.006 (0.754-1.343)	*0.966*
Hematuria level	1.456 (1.069-1.982)	***0.017***
Presence of Additional Risk Factors for UC	1.327 (0.821-2.144)	*0.248*
Microhematuria risk stratification	2.891 (0.804-10.395)	*0.104*

RR: estimated relative risk represented by odds ratio, CI: confidence interval, UC: Urothelial Ca.

the amount of smoking and both tumor stage and grade (r = 0.190, $p < 0.001$; r = 0.212, $p < 0.001$, respectively). A weak positive correlation was also found between the level of hematuria and tumor stage, tumor grade, and AUA risk category, all of which were statistically significant (r = 0.303, $p < 0.001$; r = 0.265, $p < 0.001$; r = 0.318, $p < 0.001$, respectively). The correlations of other parameters are presented in detail in Table 3.

Binary logistic regression analysis was used to identify the possible independent predictors of muscle invasion in bladder tumors that contributed the most to the outcome. Age, gender, smoking history (pack-years), hematuria level, and additional risk factors for UC, and

microhematuria risk stratification were evaluated as predictors for muscle invasion. The model predicting muscle invasion was not statistically significant (χ^2 (8) = 6.7, p = 0.564). However, the model correctly predicted the presence of muscle invasion 76.1% of the time. Among the predictors, hematuria level emerged as the most significant factor for muscle invasion (p = 0.017). In the hematuria level grouping, each step to a higher category resulted in a 1.57-fold increase in the likelihood of muscle invasion (Table 4).

4. Discussion

Bladder cancer typically presents with hematuria in 80% of cases, with macroscopic hematuria occurring more frequently than microscopic hematuria. Moreover, macroscopic hematuria is associated with a more advanced disease stage at the time of diagnosis compared to microscopic hematuria [9].

Microscopic hematuria can also result from conditions other than bladder cancer, including genitourinary malignancies, medical kidney diseases, gynecologic issues, non-malignant genitourinary causes, and the use of anticoagulant medications. To address these various factors, the AUA has published guidelines to assess the relationship between microscopic hematuria and bladder cancer. These guidelines help determine the risk of bladder cancer in patients with microscopic hematuria and provide management strategies based on these risk categories [3].

In our study, we aimed to investigate the relationship between different risk groups and bladder cancer, taking into account the levels of microscopic hematuria and the risk categories outlined in the AUA guidelines.

A 2015 study, which examined the relationship between hematuria severity at diagnosis and disease stage, found that patients visiting the health centers with macroscopic hematuria were diagnosed at more advanced stages of the disease. On the other hand, early detection in patients without macroscopic hematuria could lead to diagnosis at earlier stages. The same study reported that macroscopic hematuria was a significant predictor of muscle-invasive disease (≥T2) at diagnosis, based on both multivariate and univariate logistic regression analysis. In this study, hematuria was categorized only as macroscopic or microscopic [10].

We think that the qualitative grouping based on whether the presence of hematuria is macroscopic or microscopic should be excluded and the presence and level of hematuria should be evaluated quantitatively. This approach is supported by the current AUA guidelines [3]. In our study, we classified hematuria according to the AUA risk classification, using objective numerical data rather than subjective assessments. This method, we believe, minimizes potential biases or distortions that could arise from either patient or physician interpretations during anamnesis. Our binary logistic regression analysis, aimed at predicting muscle invasion, revealed that the most significant predictor for the presence of muscle-invasive disease was the level of hematuria.

In the 2015 study by Ramirez et al., patients were categorized based on their use of anticoagulants [10], and the relationship between high-stage disease and anticoagulant use was explored. However, the current AUA guidelines stress that patients should not be separated based on anticoagulant or antiplatelet use when assessing microscopic hematuria. Instead, the evaluation should be consistent across both groups—those who use these medications and those who do not. In line with these guidelines, our study evaluated patients collectively, rather than separately based on their medication use. Therefore, we believe that the statistical analysis

in our study is more reliable and aligned with the current literature.

Another study investigating the relationship between microscopic hematuria and bladder cancer risk found that the severity of microhematuria, smoking status, and increasing age were all associated with an elevated risk of bladder cancer [11].

Smoking is well-established as one of the most significant risk factors for bladder cancer. A cohort study conducted in 2020, which included 367,058 participants, found that 44.4% of bladder cancers were associated with smoking [12]. Numerous studies have further explored the connection between smoking and bladder cancer. For instance, a 2015 study categorized patients into three groups based on smoking history: non-smokers, light smokers (≤30 pack/year), and heavy smokers (>30 pack/year) and examined the relationship between these groups and presentation with muscle-invasive bladder cancer at the time of diagnosis. This study found that heavy smokers had a significantly higher risk of presenting with muscle-invasive bladder cancer at diagnosis [13].

A study examining the impact of smoking and cumulative smoking exposure on the recurrence of non-muscle invasive bladder cancer reported that cumulative smoking exposure was significantly associated with tumor recurrence in both current and former smokers. In their study, smoking exposure was quantified by calculating the total number of cigarettes smoked per day, multiplied by the number of years of smoking, yielding a "smoking index." The study categorized smoking exposure into high (smoking index ≥400) and low (smoking index <400) levels for analysis. However, it was unclear whether the cut-off value of 400 was supported by previous research. As such, we believe that the use of this arbitrary threshold, without confirmation from established scientific literature, weakens the validity of the analysis and its results [14].

Again, in a study examining the impact of smoking status on recurrence following transurethral resection of non-muscle invasive bladder cancer, it was found that both current and former smokers had shorter recurrence-free survival compared to non-smokers. In their study, smoking status was categorized using a cut-off of 35 pack-years [15].

We conducted our study by determining the smoking status of patients using the cut-off values recommended by the current AUA guidelines. We then compared these values both with each other and with other data in the study. This approach allowed us to analyze the clinical and pathological effects of smoking on bladder cancer, based on current scientific evidence and widely accepted classifications.

A 2021 study involving 15,779 patients also followed the current AUA guidelines. In their study, 4.6% of patients were classified in the low-risk group, 11.8% in the intermediate-risk group, and 83.6% in the high-risk group. These rates are similar to those observed in our study. Additionally, they found that bladder cancer was more prevalent among males, smokers, and individuals with macroscopic hematuria [16]. However, they did not separately evaluate the relationship between microscopic hematuria and bladder cancer pathology.

In our study, we explored the relationship between hematuria levels and bladder cancer pathology. A weak positive correlation was found between hematuria level and tumor stage, tumor grade, and AUA risk category, all of which were statistically significant. Furthermore, the factors influencing muscle invasion in bladder cancer were investigated and progressing to a higher hematuria group was determined to result in a 1.57-fold increase in the likelihood of muscle invasion. This finding statistically confirms the

association between hematuria level and muscle invasion in bladder cancer.

There are some limitations to our study. These can be listed as being retrospective, being a single-center study, urine analysis may show technical differences, and not being generalizable because it is a single-center study.

4.1. Conclusion: Hematuria level is associated with tumor grade, tumor stage, and muscle invasion in bladder cancer. Given this association, it is crucial to carefully assess hematuria levels and the microhematuria risk classifications of patients. Based on these evaluations, appropriate diagnostic and treatment strategies should be implemented. It should not be forgotten that high hematuria levels may be associated with high grade and stage in the diagnosis of bladder cancer and appropriate screening and imaging methods should be applied.

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Ethical Statement: *This study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (2011-KAEK-2, 2024/511). All methods were carried out in accordance with relevant guidelines and regulations of Helsinki declaration. Written informed consent was obtained from the participants parents or legal guardian included in the study.*

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