DOI: 10.4149/BLL_2023_112

Bratisl Med J 2023; 124 (10)
738 – 741

CLINICAL STUDY

Risk of genitourinary malignancy in patients that receive anticoagulant or antiplatelet therapy

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ABSTRACT

OBJECTIVES: Haematuria is a common indication for a urology evaluation. In many cases, its cause is not determined unequivocally, but it does not pose any threat to the patient. However, it can represent the first symptom of urinary tract cancer.

BACKGROUND: The present study aimed to compare the risk of urological malignancies in patients with haematuria who received antiplatelet or anticoagulant therapy versus those who did not.

METHODS: This prospective study included 562 patients with haematuria during the period of 2018–2021. Among these, 129 patients had macroscopic haematuria. All patients underwent a urinary tract ultrasound, CT with urography, and cystoscopy. Patients with suspected malignancy underwent an appropriate surgical procedure with a pathology examination. Data were analysed with univariate and multiple logistic regression.

RESULTS: The incidence rates of malignancies were 21.5 % overall, and 44.2 % and 14.8 % among patients with macroscopic and microscopic haematuria, respectively. Univariate regression showed that the odds of malignancy was significantly higher among patients with antiplatelet therapy compared to patients without antiplatelet therapy (OR: 1.88, 95% CI: 1.14–3.05). In contrast, anticoagulation therapy did not significantly increase the odds of malignancy compared to no anticoagulation therapy (OR: 1.45, 95% CI: 0.74–2.69). However, a multiple logistic regression model that included other known risk factors (e.g., sex or age) showed similar odds of malignancy among these patient groups.

CONCLUSIONS*:* Malignancy risk for patients who received anticoagulant or antiplatelet therapy was similar to the risk observed in the general population. Antiplatelet and anticoagulant therapy were not significant risk factors of urological malignancy in patients with haematuria. The results from the present study will be used in a power analysis for an upcoming multicentre study *(Tab. 4, Ref. 17)*. Text in PDF *www.elis.sk*

KEY WORDS: anticoagulation therapy, antiplatelet therapy, cancer, haematuria, risk factor.

Introduction

Haematuria is a common indication for a urology examination. Population studies have shown microscopic haematuria prevalence rates in the range of 0.19–16.1 %, and the prevalence increases with age (1). The incidence of urinary tract malignancies among patients with microscopic haematuria is 3.1 % (2). However, other studies have reported that the incidence of malignancy among patients with haematuria ranged from 0 to 25.8 % (3), and the risk of malignancy among patients with macroscopic haematuria was three- to four-fold higher (4). There is a clear consensus that every patient with haematuria should be evaluated. The standard evaluation comprises a CT with urography and cystoscopy in patients older than 35 years (3), but only 9–36 % of patients with haematuria are fully evaluated (5).

It remains controversial how to proceed for patients with haematuria that are receiving some sort of antithrombotic therapy. Due to the spread of diseases of civilization and aging of population, the number of patients exposed to anticoagulation or antiplatelet therapy is increasing. These antithrombotics are given either to prevent cardiovascular or cerebrovascular disease or to treat thromboembolic disease. Every year, a number of cardiac surgeries such as coronary artery bypass grafting procedures (CABG) or heart valve procedures are performed, requiring subsequent administration of anticoagulant therapy (6). For example, during the period of 2005-2016, in Germany, prescriptions for anticoagulation or antiplatelet medications increased by 136 % (7). Up to 40 % of patients treated with anticoagulants have microscopic haema-

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Acknowledgement: Supported by MH CZ – DRO (FNOs/2022).

turia (4). This finding gave rise to the hypothesis that these patients may have a lower risk of severe urinary tract disease and haematuria is only an adverse effect of therapy. Several studies have investigated this hypothesis, but most of them evaluated patients with macroscopic haematuria (7, 8, 9, 10).

The present study aimed to evaluate the risk of urological malignancies among patients with haematuria (macroscopic or microscopic), and to compare the risk between those treated with antiplatelet or anticoagulant therapy and those not treated with such therapy.

Patients and methods

This prospective study was conducted at tertiary academic centres, in accordance with the principles of the Declaration of Helsinki, World Medical Association, and Good Clinical Practice. The study protocol, patient information, and informed consent forms were approved by an independent Institutional Review Board of the University Hospital Ostrava (n. 332/2018).

Study population

From April 2018 to December 2021, the study prospectively included a total of 562 consecutive patients, over 18 years old, with microscopic or macroscopic haematuria. Microscopic haematuria was defined as the presence of more than five red blood cells per high-power field on urinalysis. Urine samples were obtained by spontaneous urination in men or by catheterization in women. Macroscopic haematuria was defined as any haematuria that could be observed by the naked eye. Patients were divided into the two treatment groups, namely those exposed to antiplatelet or anticoagulant therapy and those not exposed to either therapy. To shorten the study period, we combined all patients treated with antiplatelet or anticoagulant therapy or with a combination of medications into one group that was exposed to antithrombotic therapy.

Exclusion criteria were as follows: a proven urinary tract infection, known nephrological disease, previous radiotherapy of the pelvis, and a previously known urological malignancy.

The evaluation included a medical history and physical exam, medication history, and the presence of risk factors, such as smoking or exposure to carcinogenic substances. A properly performed urinalysis eventually ruled out a urinary tract infection. Subsequently, patients underwent a urinary tract ultrasound, cystoscopy, and computed tomography with urography.

Patients with a suspected malignancy underwent surgery, according to the type of tumour. Only patients with a histologically proven malignancy were considered positive for cancer.

Statistical analysis

Numerical parameters are expressed as the median and interquartile range (IQR: the lower and upper quartiles). Categorical parameters are expressed as absolute frequencies and relative frequencies, in percentages. Mann-Whitney test or the Chi-square test of independence for contingency tables was performed for between-group comparisons. Univariate and multiple logistic regressions were performed to assess associations between risk factors and malignancy. The significance level was set to $p = 0.05$. All statistical analyses were performed with R software (R Foundation for Statistical Computing, version 4.1.2).

Results

A total of 562 patients were included in the study. Of these, 433 (77 %) had microscopic haematuria and 129 (23 %) had macroscopic haematuria, 49.1 % were male, and the median age was 68 years. In the microscopic and macroscopic haematuria groups, the average ages were 64 years and 69 years, respectively. The median age and the proportion of male patients were significantly higher (71 years and 77.5 %) in the macroscopic haematuria group than in the microscopic haematuria group (66 years and 40.6 %).

Of all the included patients, 29.6 % used some form of antithrombotic therapy. Significantly more patients in the macroscopic haematuria group (46.5 %) used antithrombotic therapy than in the microscopic haematuria group (24.4 %).

In our study population, 121 patients were diagnosed with a urological malignancy. The most frequent type of tumour was bladder cancer (n = 84, 15 %). Urothelial carcinoma of the upper urinary tract and renal cell carcinoma were diagnosed in 14 (2.5 %) and 21 (3.7 %) patients, respectively. Two patients had tumour duplicity. In both cases, the patients had bladder and renal cell carcinomas (Tab. 1).

The regression analyses of the relationship between antithrombotic medication and the risk of cancer suggested that patients treated with antithrombotic medication had a significantly higher risk of cancer compared to those not treated with antithrombotics (28.3 % vs 18.7 %, $p = 0.016$). When we examined the different types of haematuria, patients with microscopic haematuria who

Tab. 1. Characteristics of patients with microscopic or macroscopic haematuria.

Characteristic	Total (n = 562)	Macroscopic (n = 129)	Microscopic (n = 433)	p[a]
Sex (male)	276 (49.1)	100 (77.5)	176 (40.6)	<0.001
Age (years)	68 (57–75)	71 (64–78)	66 (55–74)	<0.001
Smoking (yes)	179 (31.9)	38 (29.5)	141 (32.3)	0.576
Medication				<0.001
Antiplatelet therapy	106 (18.9)	37 (28.7)	69 (15.9)	–
Anticoagulation therapy	60 (10.7)	23 (17.8)	37 (8.5)	–
None	396 (70.4)	69 (53.5)	327 (75.6)	–
Malignancies	121 (21.5)	57 (44.2)	64 (14.8)	<0.001
				0.226
Bladder cancer	84 (14.9)	40 (31.0)	44 (10.2)	–
UTUC	14 (2.5)	8 (6.2)	6 (1.4)	–
Renal cancer	21 (3.7)	7 (5.4)	14 (3.2)	–
Multiple	2 (0.4)	2 (1.6)	–	–

Values represent the median (interquartile range) or the number (%), as indicated.
p[a] – values based on the Mann-Whitney test or chi-square test of independence for contingency tables
UTUC: urothelial carcinoma of the upper urinary tract.

were treated with antithrombotics were at a significantly higher risk compared to patients treated without antithrombotics (21.7 % vs 12.5 %, p = 0.031). However, among patients with macroscopic haematuria, no difference in cancer risk was found between those treated and those not treated with antithrombotics (Tab. 2).

Next, we investigated whether the risk of urological malignancies was associated with a specific type of antithrombotic medication. We found that the risk of malignancy was only significantly different between groups with or without therapy at the level of the entire group of patients.

The univariate logistic regression results supported previous findings. A higher age, male sex, and a positive ultrasound finding were associated with significantly increased odds of malignancy. Furthermore, patients treated with antiplatelet therapy had significantly increased odds of malignancy compared to patients treated without therapy (OR: 1.88, 95% CI: 1.14–3.05) (Tab. 3). In contrast, patients treated with anticoagulation therapy did not have significantly increased odds for malignancy compared to patients treated without anticoagulation therapy (OR: 1.45, 95% CI: 0.74–2.69). However, when considering all the risk factors, the multiple logistic regression results suggested that there was no association between antithrombotic therapy and the risk (odds) of cancer (Tab. 4).

Tab. 2. Associations between cancer risk and antithrombotic medications for patients with macroscopic or microscopic haematuria.

Patient group	Cancer occurrence (risk)		p[a]
	Antithrombotic therapy	No therapy	
Total	47/166 (28.3%)	74/396 (18.7%)	0.016
Macroscopic	24/60 (40.0%)	33/69 (47.8%)	0.475
Microscopic	23/106 (21.7%)	41/327 (12.5%)	0.031

Values represent the number of patients over the total number of patients in the group, and the risk of cancer (%). p[a] – values based on the chi-square test of independence for contingency tables.

Tab. 3. Associations between cancer risk and the use of antiplatelet or anticoagulation therapy for patients with macroscopic or microscopic haematuria.

Patient group	Cancer occurrence (risk)			p[a]
	Antiplatelet therapy	Anticoagulation therapy	None	
Total	32/106 (30.2%)	15/60 (25.0%)	74/396 (18.7%)	0.030
Macroscopic	18/37 (48.6%)	6/23 (26.1%)	33/69 (47.8%)	0.155
Microscopic	14/69 (20.3%)	9/37 (24.3%)	41/327 (12.5%)	0.060

Values represent the number of individuals with cancer divided by the total number of patients in the group and the risk of cancer (%). p[a] – values based on the Chi-square test of independence for contingency tables.

Tab. 4. Univariate and multiple logistic regression results identify risk factors for cancer occurrence among patients with haematuria.

Risk factor	Univariate Logistic Regression		Multiple Logistic Regression	
	OR (95%CI)	p	OR (95%CI)	p
Age (years)	1.04 (1.02–1.07)	<0.001	1.06 (1.03–1.10)	<0.001
Haematuria type				
Macroscopic	4.56 (2.95–7.09)	<0.001	2.12 (1.22–3.65)	0.007
Microscopic	Reference	–	Reference	–
Sex				
Male	4.43 (2.83–7.11)	<0.001	3.08 (1.78–5.46)	<0.001
Female	Reference	–	Reference	–
Smoking				
Yes	1.07 (0.69–1.64)	0.748	1.46 (0.82–2.56)	0.191
No	Reference	–	Reference	–
Therapy				
Antiplatelet	1.88 (1.14–3.05)	0.011	0.87 (0.45–1.62)	0.665
Anticoagulation	1.45 (0.74–2.69)	0.252	0.48 (0.20–1.09)	0.091
None	Reference	–	Reference	–
Ultrasound				
Positive for cancer	35.43 (16.35–88.71)	<0.001	36.68 (15.58–99.31)	<0.001
Negative for cancer	Reference	–	Reference	–

OR: Odds ratio; 95% CI: 95% confidence interval

Discussion

Our results showed that, among patients with macroscopic haematuria, the proportion of malignancies was high, namely over 44 %. In the group of microscopic haematuria, our findings (14 %) were more consistent with those of other studies, which indicated an incidence of around 10–20 % (11, 12). Nevertheless, we could not fully explain the high numbers of malignancies in both groups. We speculate that the results may be attributed to the COVID-19 pandemic, which has altered the spectrum of patients that were evaluated. In terms of tumour type, bladder cancer was diagnosed most frequently in our cohort (around 40 % in both groups), consistent with previous studies (13).

In our study population, the use of antiplatelet therapy initially showed to be a significant risk factor in the simple analysis. However, upon incorporating additional variables, the significance diminished, and it was determined that age and male sex were the primary factors affecting the patient risk. The initial significance observed in the simple analysis, could be attributed to the nearly two-fold higher number of men in the antithrombotic therapy group as compared to the no-therapy group. Thus, we identified male sex as a confounding factor. Nonetheless, our results reaffirmed that haematuria warranted a standard evaluation irrespective of the medication taken.

Previous studies showed that the prevalence of microscopic haematuria ranged from 0.2 to 18 % and increased with age (3, 14). Among patients with haematuria, 70–90 % had no serious urological disease (15). The risk of malignancy was in the range of 0–11 % in various studies (3, 13). Nevertheless, the necessity of a standard evaluation for patients with haematuria, especially macroscopic haematuria, has been generally accepted; however, for example, the Swedish Group does not recommend evaluations for patients with microscopic haematuria (16). Moreover, the recommendations are not different for patients who receive some form of antithrombotic therapy (3). However, that

recommendation was supported by studies that mostly included patients with macroscopic haematuria.

The American Urological Association (AUA) guidelines for microscopic haematuria recommend a cystoscopy for patients over 35 years of age. In patients younger than 35 years, the risk of malignancy was reported to be increased, up to 1.2 % (3). Tan et al. found out that even though the risk of malignancy was small, most patients were willing to undergo an invasive procedure (13); therefore, we performed a complete haematuria evaluation in all patients older than 18 years. In our cohort, among the patients younger than 35 years, only one in each group had a proven malignancy. Those numbers represented 0.88 % of the macroscopic haematuria group and 0.23 % of the microscopic haematuria group.

The increase in the number of patients receiving anticoagulant and antiplatelet therapy can be attributed to population aging and with advancements in cardiovascular disease therapy. Among patients on anticoagulant therapy, 12–40 % have haematuria (10). Bhatt et al reported a 24 % risk of malignancy among patients that received antithrombotic therapy, but that group had macroscopic haematuria (17).

In a previous retrospective study that included patients older than 66 years, Wallis et al. reported a higher risk of bladder cancer among patients who received antithrombotic therapy compared to those that did not. In studies on other urological malignancies, this association has not been reported (9). In our study population, the risk of bladder cancer did not differ between the group that received antithrombotic therapy and the group not receiving such therapy.

We could not explain why our macroscopic haematuria group included such a high number of patients with malignancy. In other studies, the reported numbers were, at most, half of the current study's findings (12). The greatest limitation of our study was the relatively small number of patients in the two haematuria groups, particularly when we evaluated the antiplatelet and anticoagulant therapy subgroups separately. Moreover, our study took place partly during the COVID-19 pandemic. During this period, we noted a reduction in the number of patients with microscopic haematuria and an increase in the number of patients with macroscopic haematuria, and often, with advanced disease. This finding resulted from the nature of the pandemic period. The findings of the present study will be utilised in a power analysis for an upcoming multicentre study.

Conclusion

The risk of urological malignancy in patients with haematuria who received antithrombotic therapy was comparable to the risk observed in the population not treated with such therapy. Antithrombotic therapy did not represent a risk factor for the occurrence of malignancies in patients with haematuria. Findings of the present study will be utilised in a power analysis for an upcoming multicentre study.

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Received April 3, 2023.
Accepted April 17, 2023.