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Evaluation of the New American Urological Association Guidelines Risk Classification for Hematuria

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Purpose: Microhematuria is a prevalent condition and the American Urological Association has developed a new risk-stratified approach for the evaluation of patients with microhematuria. Our objective was to provide the first evaluation of this important guideline.

Materials and Methods: This multinational cohort study combines contemporary patients from 5 clinical trials and 2 prospective registries who underwent urological evaluation for hematuria. Patients were stratified into American Urological Association risk strata (low, intermediate or high risk) based on sex, age, degree of hematuria, and smoking history. The primary end point was the incidence of bladder cancer within each risk stratum.

Results: A total of 15,779 patients were included in the analysis. Overall, 727 patients (4.6%) were classified as low risk, 1,863 patients (11.8%) were classified as intermediate risk, and 13,189 patients (83.6%) were classified as high risk. The predominance of high risk patients was consistent across all cohorts. A total of 857 bladder cancers were diagnosed with a bladder cancer incidence of 5.4%. Bladder cancer was more prevalent in men, smokers, older patients and patients with gross hematuria. The cancer incidence for low, intermediate and high risk groups was 0.4% (3 patients), 1.0% (18 patients) and 6.3% (836 patients), respectively.

Conclusions: The new risk stratification system separates hematuria patients into clinically meaningful categories with differing likelihoods of bladder cancer that would justify evaluating the low, intermediate and high risk groups with incremental intensity. Furthermore, it provides the relative incidence of bladder cancer in each risk group which should facilitate patient counseling regarding the risks and benefits of evaluation for bladder cancer.

Abbreviations and Acronyms

AUA = American Urological Association
CT = computerized tomography
HPF = high powered field
RBC = red blood cell

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Key Words: urinary bladder neoplasms, hematuria, guidelines as topic, evaluation study

MICROHEMATURIA is a common condition, with a prevalence of 6.5% among healthy volunteers and a range from 2.4% to 31.1% depending on the population studied.[1] However, the rate of genitourinary malignancy diagnosed among patients with microhematuria is approximately 3% (range 0.3% to

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6.25%), and, importantly, cancer risk has been shown to vary with patient factors among referred populations.[1] The 2012 American Urological Association asymptomatic microhematuria guideline recommended evaluation with CT urography and cystoscopy in all patients over 35 years of age with microhematuria defined as ≥3 red blood cells per high powered field.[1] The goal of this approach was to minimize the number of missed cancers. Indeed, a model comparing evaluation recommendations according to the AUA with other international guidelines found that the AUA guideline had the lowest likelihood of missing detection of cancer.[2] Nevertheless, cystoscopy is a relatively invasive procedure which may be associated with discomfort and urinary infection risk, while CT urography may be associated with contrast reactions, radiation exposure, the additional testing sequalae of false-positive results, as well as significant health system costs.[2]

Moreover, multiple series have documented a low rate of compliance with the recommended diagnostic testing for patients with microhematuria,[3–6] particularly among women. The potential consequences of a delayed or incomplete hematuria evaluation includes delay of diagnosis of malignancy. Women have more advanced tumors at the time of bladder cancer diagnosis, which may be related to such delays.[7] Many patients with microhematuria already have invasive disease but it is likely that most patients have microhematuria prior to gross hematuria. As such, it is plausible that this represents a window of opportunity to identify disease earlier.[8,9]

In this context, the AUA in collaboration with the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction recently developed a new, risk based guideline that stratifies patients as low, intermediate and high risk for urological malignancy.[10] The panel included recognized risk factors for urothelial carcinoma including age, gender, tobacco exposure, degree of hematuria (gross hematuria versus microhematuria), and number of red blood cells per HPF as well as occupational and environmental factors, family history, prior pelvic radiation, and cyclophosphamide exposure.[11] The risk stratification system was developed from a review of the literature and with expert opinion input, but remains unvalidated. The guideline also does not identify the rate of malignancy in the new risk groupings, which would allow providers to counsel patients of the likelihood of cancer based on their personalized risk.

The objective of this study is to validate that the risk stratification system accurately stratifies patients into clinically meaningful categories, with differing likelihoods of bladder cancer that would justify evaluating the low, intermediate and high risk groups with incremental intensity. In order to achieve that goal, we determined the likelihood of bladder cancer within each risk stratum using a large group of patients with hematuria who were evaluated as part of prospective studies.

METHODS

We utilized data from 7 patient cohorts who underwent cystoscopic evaluation of hematuria. These cohorts included 5 clinical trials investigating the role of various urine markers in the evaluation of patients with hematuria (cohorts B,[12] C,[13,14] D,[15] E,[16] F[17]) and 2 prospective registries (cohorts A[9] and G[4]). Details on the cohorts are available in the supplementary Appendix (https://www.jurology.com). Requirements for cohort inclusion were available data for risk stratification (age, sex, gross vs microhematuria, and smoking status) as well as evaluation with cystoscopy. The primary endpoint was the incidence of bladder cancer detection, assessed in the overall population studied and in each of the new AUA Guideline risk groups (see Appendix).[10] Bladder cancer diagnosis was based on pathological confirmation. In addition, some data sets included discrete data on smoking intensity (ie number of pack-years of smoking), which were incorporated into stratification when available (supplementary table, https://www.jurology.com). When these data were missing, patients were stratified based on age and sex alone as well as presence of gross vs microhematuria. Descriptive statistics were used to compare risk-stratified groups. Chi-square testing was used to compare categorical variables and 1-way analysis of variance was used to compare means. Tests were 2-sided, and findings were considered significant at $p < 0.05$. Analysis was performed using SPSS version 25.0 (IBM Co., Armonk, New York).

RESULTS

A total of 15,779 patients were included in the study. Details of patient characteristics in each cohort are reported in table 1. The mean (SD) age was 60.9 (14.6) years and 53% of the patients were male. Race was not reported in 63.5% of cases, but when reported, the majority (86.5%) of patients were White, while 5.6% were Black, 3.6% Hispanic and 4.2% Asian. Smoking status was never smoker (52.8%), former/current (44.9%) and unknown in 2.2%. Hematuria status was gross hematuria (35.7%), microhematuria (62.0%) and unknown in 2.3%. There was a total of 727 patients (4.6%) classified as low risk, 1,863 patients (11.8%) classified as intermediate risk and 13,189 patients (83.6%) classified as high risk. All cohorts had a predominance of patients classified as high risk (range 53%–89%), with moderate variability as illustrated in figure 1, *A*.

Overall, 857 bladder cancers were diagnosed for a bladder cancer detection rate of 5.4% in the entire cohort, with a moderate degree of variability between the cohorts ranging from 2.3% to 11.5% (fig. 1, *B*).

Comparison of Risk Groups

As can be expected by definitions of risk stratification, age, degree of hematuria and smoking status

Table 1. *Description of patients in cohorts*

	Overall		Cohort													
			A		B		C		D		E		F		G	
No. pts (%)	15,779		3,556	(22.5)	1,217	(7.7)	1,385	(8.8)	1,005	(6.4)	906	(5.7)	378	(2.4)	7,332	(46.5)
Mean yrs age (SD)	60.9	(14.6)	65.70	(13.9)	58.37	(14.3)	64.20	(13.2)	62.71	(15.1)	62.48	(13.7)	59.64	(14.0)	57.95	(14.5)
No. sex (%):																
Male	8,376	(53.1)	2,112	(59.4)	674	(55.4)	910	(65.7)	608	(60.5)	521	(57.5)	186	(49.2)	3,365	(45.9)
Female	7,403	(46.9)	1,444	(40.6)	543	(44.6)	475	(34.3)	397	(39.5)	385	(42.5)	192	(50.8)	3,967	(54.1)
No. degree of hematuria (%):																
Microhematuria	9,777	(62.0)	1,108	(31.2)	1,004	(82.5)	606	(43.8)	463	(46.1)	422	(46.6)	176	(46.6)	5,998	(81.8)
Gross hematuria	5,640	(35.7)	2,086	(58.7)	213	(17.5)	779	(56.2)	542	(53.9)	484	(53.4)	202	(53.4)	1,334	(18.2)
Unknown	362	(2.3)	362	(10.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
No. smoking status (%):																
Never	8,339	(52.8)	1,528	(43.0)	798	(65.6)	669	(48.3)	313	(31.1)	434	(47.9)	187	(49.5)	4,410	(60.1)
Former/current	7,088	(44.9)	1,879	(52.8)	419	(34.4)	715	(51.6)	491	(48.9)	472	(52.1)	190	(50.3)	2,922	(39.9)
Unknown	352	(2.2)	149	(4.2)	0	(0.0)	1	(0.1)	201	(20.0)	0	(0.0)	1	(0.3)	0	(0.0)
No. risk group (%):																
Low	727	(4.6)	106	(3.0)	221	(18.2)	57	(4.1)	84	(8.4)	45	(5.0)	12	(3.2)	202	(2.8)
Intermediate	1,863	(11.8)	282	(7.9)	348	(28.6)	163	(11.8)	129	(12.8)	134	(14.8)	69	(18.3)	738	(10.1)
High	13,189	(83.6)	3,168	(89.1)	648	(53.2)	1,165	(84.1)	792	(78.8)	727	(80.2)	297	(78.6)	6,392	(87.2)
No. Ca incidence (%)	857	(5.4)	288	(8.1)	76	(6.2)	112	(8.1)	116	(11.5)	74	(8.2)	21	(5.6)	170	(2.3)

varied among the risk groupings ($p < 0.01$). Additionally, there was a higher percentage of women in the low risk group (80.3%) and a higher proportion of men in the high risk group (54.8%, $p < 0.01$). Cancer incidence varied according to risk stratification (table 2, fig. 2).

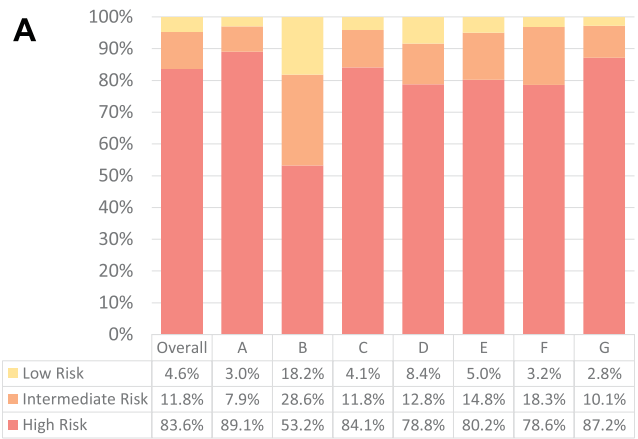

Figure 1. *A*, risk stratification across cohorts. *B*, bladder cancer incidence across cohorts.

Within each risk grouping, sex and smoking were associated with likelihood of cancer with a higher rate among men and smokers.

Low Risk Stratum

Of the 727 patients in the low risk stratum, the cancer incidence was 0.4% (3 patients). The mean (SD) age in the low risk stratum was 38.7 (7.4) years and 80.3% of patients were female. By definition, no patients had gross hematuria, and 28.9% were current or former smokers.

Intermediate Risk Stratum

Of the 1,863 patients in the intermediate risk stratum, the cancer incidence was 1.0% (95% CI 0.6–1.5, 18 patients). The mean (SD) age in the intermediate risk stratum was 51.7 (6.4) years and 45.9% were female. By definition, no patients had gross hematuria, and 43.3% were current or former smokers.

High Risk Stratum

Of the 13,189 patients in the high risk stratum, the cancer incidence 6.3% (836 patients). The mean (SD) age in the high risk strata was 63.4 (14.1) years and 45.2% were female. Among high risk patients, cancer incidence was higher in men (9.3% vs 2.8%, $p < 0.01$), and those with a smoking history vs never smokers (9.1% vs 3.7%, $p < 0.01$; table 3). Of 7,296 patients in the high risk group who had microhematuria, cancer incidence was 2.6% (95% CI 2.3–3.0), while of the 5,640 patients with gross hematuria the cancer incidence was 10.9% (95% CI 10.1–11.7), $p < 0.01$ (fig. 2).

DISCUSSION

In this study, we compiled a robust data source of over 15,000 patients from diverse cohorts, including prospective registries and clinical trials, to validate this

Table 2. *Comparison of risk groups in overall study population*

	Risk Grouping			
	Low	Intermediate	High	p Value
Mean yrs age (SD)	38.7 (7.4)	51.7 (6.4)	63.4 (14.1)	-
No. sex (%):				
Male	143 (19.7)	1,007 (54.1)	7,226 (54.8)	<0.01
Female	584 (80.3)	856 (45.9)	5,963 (45.2)	
No. degree of hematuria (%):				
Microhematuria	694 (95.5)	1,787 (95.9)	7,296 (55.4)	<0.01
Gross hematuria	0 (0.0)	0 (0.0)	5,640 (42.8)	
Unknown	33 (4.5)	76 (4.1)	253 (1.9)	
No. smoking status (%):				
Never	490 (67.4)	1,007 (54.1)	6,842 (51.9)	<0.01
Former/current	210 (28.9)	806 (43.3)	6,072 (46.0)	
Unknown	27 (3.7)	50 (2.7)	275 (2.1)	
No. Ca incidence (%)	3 (0.4)	18 (1.0)	836 (6.3)	<0.01

new risk-stratified approach to the AUA hematuria guidelines by determining the rate of cancer detection within each new risk stratum. Several key findings emerge from the analyses herein. First, we validated the risk groupings used in the new AUA guidelines, demonstrating that the rate of cancer was highly correlated with the risk classification, as bladder cancer was diagnosed in 0.4%, 1.0% and 6.3% of low, intermediate and high risk groups, respectively. These data provide useful information for clinicians and patients to make decisions regarding evaluation of patients with hematuria. Furthermore, only 0.4% of all cancers were in the low risk group such that even if every patient with low risk factors opted for observation the rate of missed cancer would be incredibly low. The known risk factors for bladder cancer, including increasing age, male sex, smoking and gross hematuria, were all associated with an increased incidence. Their use in risk stratification in the guidelines leads to a good segregation of high risk patients with 98% of all cancers in the high risk grouping.

A second, perhaps serendipitous, observation from the data set collected here is that primary care providers already have a significant referral bias in selecting patients for hematuria evaluation. That is, despite the fact that our data came from different

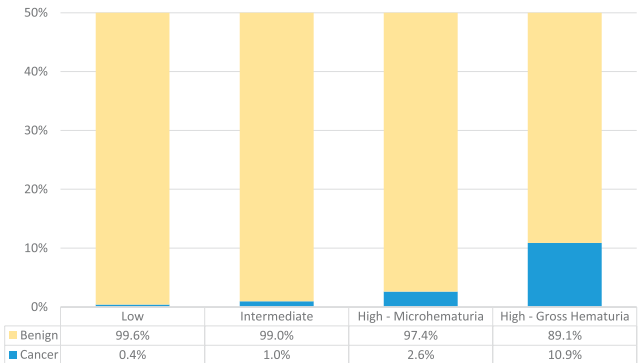

Figure 2. Bladder cancer incidence by risk group

settings, including U.S. and international sites, and from academic, community and county hospitals, there were very similar rates of low, intermediate and high risk groups between the cohorts, with the preponderance of patients from all groups in the high risk group. Indeed, 84% of our entire study population was considered high risk, while just 12% and 4.6% were considered intermediate and low risk, respectively. While it appears that many primary care physicians are already identifying patients with risk factors for bladder cancer and referring them at higher rates, we and others have previously reported on a suboptimal referral for evaluation of high risk patients with hematuria—and there is an opportunity to improve compliance with these more judicious guidelines.[4,18,19]

A third potential implication from the results here is that evaluation may be even further refined in the future, either by optimizing clinical factors or through the use of urine based tumor markers. These are specific areas noted in the future directions section of the guidelines. For example, the intermediate risk group of the guidelines only had a 1.0% bladder cancer detection rate overall, which in women was 0.6%. Likewise, in the high risk group, patients who had microhematuria alone had 2.6% cancer detection. While the guidelines recommend cystoscopy for all such patients, the opportunity exists to determine if some of these patients could also avoid invasive testing. A prospective study would be necessary to determine if certain risk factors need to be weighted differently, or could be used in conjunction with a urine based marker. For example, sex and smoking both impacted risk of bladder cancer yet a woman over the age of 60 who is a nonsmoker and has only microscopic hematuria even 3 RBC/HPF is currently considered high risk. The current guidelines do not recommend the use of urine based tumor markers because their clinical utility has not been validated, however, multiple markers have a very high negative predictive value.[12–15,20] Futures studies will be necessary to determine if a patient with

Table 3. *Cancer incidence among subgroups stratified by risk grouping*

	Risk Grouping					
	Low		Intermediate		High	
	No. Diagnosed with Ca (% evaluated)	p Value	No. Diagnosed with Ca (% evaluated)	p Value	No. Diagnosed with Ca (% evaluated)	p Value
Sex:						
Male	1 (0.7)	0.55	13 (1.3)	0.12	670 (9.3)	<0.01
Female	2 (0.3)		5 (0.6)		166 (2.8)	
Degree of hematuria:						
Microhematuria	3 (0.4)	0.71	17 (1.0)	0.75	190 (2.6)	<0.01
Gross hematuria	-		-		614 (10.9)	
Unknown	0		1 (1.3)		32 (12.6)	
Smoking status:						
Never	1 (0.2)	0.35	10 (1.0)	0.78	256 (3.7)	<0.01
Former/current	2 (1.0)		8 (1.0)		553 (9.1)	
Unknown	0		0		27 (9.8)	

microhematuria and a negative marker may be able to avoid cystoscopy.

Limitations of our analysis include an incomplete assessment of all risk factors for bladder cancer (eg most cohorts are missing data on occupational hazards, irritative voiding symptoms). Additionally, we focus our assessment on bladder cancer risk as it the most common concern during hematuria evaluation. The AUA guidelines make recommendations about upper tract imaging based on risk stratification which are not addressed in the present study as we did not have a complete accounting of results of upper tract imaging, which can rarely identify upper urinary tract malignancy, renal cortical tumors, and other benign urological conditions (eg urolithiasis). While we report on cancer rates in each risk grouping, the true incidence of cancer in microhematuria patients is still unknown, as the reported rates are in referred populations, but as noted above many patients with hematuria are not referred for urological evaluation. In a large managed care organization (Kaiser Permanente), only 7,778 (1.7%) patients were seen by a urologist out of 456,674 who had microscopic hematuria.[4,19] This pattern of low rates of referral is seen in multiple health care settings.[19,21] As such, rates of cancer in our study may be higher than the true incidence if one were to include patients who were not referred. An additional limitation is the inability to incorporate exact RBCs/HPF into the risk stratification. While this may theoretically change the distribution of risk stratification in patients with pure microhematuria, the vast majority of patients were upgraded to higher risk strata by their age, gender or smoking status. If there were to be an impact, this would likely upgrade some lower risk category to a higher risk category and likely depress the already low incidence of malignancy detection in the low risk category.

The strengths of this study were that every patient underwent cystoscopic evaluation, which is the current gold standard for detecting bladder cancer. Additionally, the study population represents a large and diverse cohort of patients from well-annotated and prospective studies, which may approximate the significant heterogeneity in the patients that present to a urologist's clinic for evaluation of hematuria.

CONCLUSIONS

Our study of over 15,000 patients with hematuria who underwent cystoscopy validated that the risk stratification system separates microhematuria patients into clinically meaningful categories, with differing likelihoods of bladder cancer that would justify evaluating the low, intermediate and high risk groups with incremental intensity. Our study provides the relative incidence of bladder cancer in each risk group that should facilitate patient counseling regarding the risks and benefits of evaluation for bladder cancer.

Appendix. *AUA microhematuria risk stratification system (revised 2020)*[10]

Low (patient meets all criteria)	Intermediate (patient meets any one of these criteria)	High (patient meets any one of these criteria)
Women age <50 years; Men age <40 years	Women age 50–59 years; Men age 40–59 years	Women or Men age >60 years
Never smoker or <10 pack years	10–30 pack years	>30 pack years
3–10 RBC/HPF on a single urinalysis	11–25 RBC/HPF on a single urinalysis	>25 RBC/HPF on a single urinalysis
No risk factors for urothelial cancer (see table 2)	Low risk patient with no prior evaluation and 3–10 RBC/HPF on repeat urinalysis	History of gross hematuria
	Additional Risk factors for urothelial cancer*	

*Irritative lower urinary tract symptoms, prior pelvic radiation, prior cyclophosphamide/ifosfamide chemotherapy, familial history of urothelial cancer of Lynch Syndrome, occupational exposures to benzene chemicals or aromatic amines, chronic indwelling foreign body in the urinary tract.

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EDITORIAL COMMENT

With the May 2020 release of updated microhematuria guideline recommendations, the AUA took an important step towards reducing low-value diagnostic evaluations. The new stratified approach was driven by improved knowledge of cancer risk factors and is supported by comparative effectiveness research that sheds light on the exorbitant cost of finding incremental cancers as well as the harms inflicted by our attempts to do so.[1] However, in the absence of validation, the question remains—did the AUA go too far or not far enough with these changes?

Woldu et al begin to answer this question by evaluating the frequency of bladder cancer diagnoses in patients with hematuria stratified according to AUA risk category. This analysis of nearly 16,000 patients had an overall bladder cancer incidence of >5% and found reasonable differences in incidence among individual risk groups. However, a fundamental problem in the microhematuria literature is denominator neglect and this study is no different. While pragmatic, assessing cancer incidence among patients already evaluated by a urologist will always overestimate the true proportion of adults with microhematuria who harbor urological cancers. Prior estimates indicate that in real-world practice very few patients with microhematuria are ever evaluated by a urologist (reference 5 in article). Therefore, the true incidence of cancer is probably much lower than current estimates, especially when considering the referral bias inherent to these cohorts.

Despite the important contribution this manuscript makes, additional evaluation and validation studies are still needed. This study used previously published prospective databases but these did not include all the parameters used to stratify patients according to the new guidelines. Moving forward, it will be important to validate the guidelines using all components of the novel stratification algorithm, such as number of RBCs/HPF. Lastly, there are lingering questions about whether renal cortical

tumors are found during hematuria evaluations any more often than those discovered incidentally. Therefore, it is important to include kidney cancer diagnoses as an outcome in future studies in order to appropriately guide further de-implementation of CT scans in even more patients. As a field, given the high prevalence of microhematuria, we need to work towards maximizing how often we find clinically significant cancers while minimizing the costs, both human and resource-wise, of our search.

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