



Original article

## Predictors of genitourinary malignancy in patients with asymptomatic microscopic hematuria

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### Abstract

**Objectives:** To report the incidence of genitourinary malignancy and identify associated risk factors in patients undergoing urologic evaluation for asymptomatic microscopic hematuria (AMH) according to the 2012 American Urologic Association guidelines.

**Subjects/patients and methods:** A retrospective institutional review of patients who underwent evaluation for AMH between 2012 and 2015 was conducted. Covariates analyzed included age, sex, smoking status, history of other malignancy, history of pelvic irradiation, presence of irritative voiding symptoms, use of anticoagulation, number of red blood cells on microscopic urinalysis, and guideline adherence. Univariate analysis was performed to explore the association between these risk factors and the presence of genitourinary malignancy.

**Results:** Of the 1,049 patients analyzed with AMH, urologic malignancy was diagnosed in 12 patients (1.1%), including 1 upper-tract urothelial cancer, 5 renal tumors, and 6 bladder tumors. All patients with malignancy were over 50 years old. Older age, male sex, smoking history, and irritative voiding symptoms were associated with malignancy on univariate analysis.

**Conclusions:** Our data adds to the growing evidence that the incidence of malignancy among patients with AMH is low. Risk factors associated with urinary tract cancer are male sex, age > 50 years, smoking history, and irritative voiding symptoms. Further prospective, randomized trials would be useful for developing a more tailored screening protocol for low-risk patients. © 2017 Elsevier Inc. All rights reserved.

**Keywords:** Microscopic hematuria; Urothelial carcinoma; Bladder cancer; Renal cell carcinoma

### 1. Introduction

Microscopic hematuria is a relatively common clinical entity that may be a harbinger for significant urinary tract disease. Population-based studies have reported the prevalence of asymptomatic microscopic hematuria (AMH) ranging between 0.19% and 16.1% [1,2]. Although the etiology of AMH is often benign, the clinician must consider the possibility of urologic malignancy as the culprit. Of patients diagnosed with urothelial carcinoma, up to 23.1% present with microscopic hematuria [3].

While no medical organization recommends routine screening for urinary tract malignancy, guidelines have

evolved to evaluate patients with clinically detected AMH [4]. In 2001, the American Urological Association (AUA) issued a best practice policy statement recommending that patients with 3 or more red blood cells per microscopic high-powered field (RBC/HPF) from at least 2 properly collected urine specimens should be evaluated with upper-tract imaging, cystoscopy, and urine cytology [5]. The Canadian Urologic Association published similar guidelines in 2009, suggesting that upper-tract evaluation should start with renal ultrasound [6]. In 2012, the AUA published official guidelines that recommended patients with AMH be evaluated with computed tomography (CT) urography, cystoscopy in those older than 35 years or with certain risk factors, and optional urine cytology only for patients with high risk for carcinoma in situ [7]. Moreover, the threshold to perform a complete urologic evaluation was lowered to

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include all patients with 1 urinalysis (UA) demonstrating 3 or greater RBC/HPF.

The challenge of investigating AMH lies in appropriate patient selection. This requires thorough risk stratification to identify which patients are more likely to harbor significant disease. Moreover, the decision whether to obtain expensive or invasive tests necessitates balancing the risk of missing significant pathology with that of excess usage of resources and potential harms of testing.

The purpose of our study is to report the incidence of genitourinary (GU) malignancy and to identify associated risk factors in patients undergoing a urologic evaluation for AMH at our institution after the publication of the 2012 AUA guidelines.

## 2. Subjects and methods

### 2.1. Patients

A retrospective, Institutional Review Board-approved study of adult patients referred to our urology department for AMH was performed. The electronic medical record was queried to identify all patients seen for an initial visit for microscopic hematuria or hematuria, unspecified (International Classification of Diseases, Ninth Revision diagnosis codes of 599.72 and 599.70). Medical charts were individually reviewed to confirm a documented initial UA demonstrating  $\geq 3$  RBC/HPF between July 2012 and June 2015 as performed by an accredited and separate laboratory service. No microscopic UAs were performed in-house or by back office personnel. Patients evaluated before the publication of the current AUA guidelines for AMH in 2012, those without microscopic analysis or with negative microscopy (i.e., positive dipstick alone), and those with an established cause for hematuria were excluded. Patients with gross hematuria (current or previous), indwelling catheter, previous evaluation for microscopic hematuria, and those with incomplete records were also excluded. We defined “asymptomatic” as the absence of dysuria or flank pain. Given that the AUA AMH guideline authors explicitly included irritative voiding symptoms as a “common risk factor for urinary malignancy in patients with microhematuria,” we included patients with urinary frequency or urgency in our analysis. The guideline authors furthermore did not exclude patients with symptoms of benign prostate enlargement in guideline statement 2, while expressly noting that certain potential benign causes do not require evaluation [7].

### 2.2. Data

Demographics, medical history, laboratory results, and diagnostic findings were obtained from the electronic medical record. Covariates of interest included patients' age, sex, ethnicity, smoking status, history of other

malignancies, history of pelvic irradiation, presence of irritative voiding symptoms, current use of anticoagulation, degree of microscopic hematuria on UA, and provider adherence to the 2012 AUA AMH guidelines. Microscopic UAs were categorized as 3 to 5, 6 to 10, 11 to 25, 26 to 50, or greater than 50 RBC/HPF, which reflects how our laboratory reports the microscopic examination. For patients that had multiple documented UAs, only the first UA was included for data analysis.

Patients' records were reviewed for diagnoses of renal cancer, upper-tract urothelial cancer, and bladder cancer. Noncancer diagnoses found on imaging and cystoscopy were also recorded. For patients with cancer, pathology reports to determine cancer type, grade, and pathologic stage were obtained. Treatment for identified malignant and nonmalignant conditions (e.g., nephrolithiasis) were also recorded.

The type of diagnostic studies was compiled and evaluated for compliance to the current AUA AMH guidelines [7]. Rates of AUA guideline compliance were determined with each diagnostic test and overall compliance on a patient-level.

### 2.3. Statistical analysis

The chi-squared and Fisher exact tests were used to determine differences in categorical risk factors between patients diagnosed with urologic malignancy and patients not found to have urologic malignancy. The Mann-Whitney *U* test was used to assess for the difference in age between the 2 cohorts, given the assumption of nonparametric distribution. Logistic regression analysis was performed to identify any covariates of interest that were independent predictors of GU malignancy. All analyses were performed using Stata v. 14 (StataCorp LP, College Station, TX). Statistical significance was determined if the *P* value was  $< 0.05$ .

## 3. Results

A final cohort of 1,049 patients with AMH were included for analysis. The study population had a mean age of 57 years (standard deviation = 13.9), and consisted of 620 females (59.1%) and 429 males (40.9%). The remainder of the demographic and baseline clinical data is included in [Table 1](#).

While 621 (59.2%) patients had a negative workup, GU malignancy was diagnosed in 12 patients (1.1%); urolithiasis was incidentally found in 118 (11.2%) patients, although only 19 of these 118 (16.1%) underwent surgical intervention ([Table 2](#)). The remaining 298 (28.4%) patients had other benign findings such as 246 with renal cysts (23.4%), and 79 with enlarged prostate (18.4% of men).

Of the 12 patients diagnosed with GU malignancies, 1 was found to have upper-tract urothelial carcinoma

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