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Clinical-Bladder cancer

Disparities in the diagnostic evaluation of microhematuria and implications for the detection of urologic malignancy

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Abstract

Introduction: Disparities in survival for bladder and kidney cancer among the genders and patients with varying insurance coverage have been identified. Microhematuria (MH), a potential early clinical sign of genitourinary malignancy, should prompt a standardized diagnostic evaluation. However, many patients do not complete a full evaluation and may be at risk of a missed or delayed identification of genitourinary pathology.

Methods: Patients 35 and older with a new diagnosis of MH between 2007 and 2015 were retrospectively identified at a large health system. Our primary outcome of interest was completion of cystoscopy and imaging. Regression modeling was used to assess associations between gender and insurance status with completion of a MH evaluation, adjusted for clinical factors, urinalysis data, and patient demographics.

Results: Of 15,161 patients with MH, only 1,273 patients (8.4%) completed upper tract imaging and a cystoscopy; 899 (5.9%) within 1 year. Median time to imaging was 75 days and 68.5 days for cystoscopy. Of those with an incomplete evaluation, 23.7% underwent cystoscopy and 76.3% underwent imaging. Male gender, private insurance, and increased MH severity on UA were associated with a complete evaluation. More patients who completed an evaluation were diagnosed with bladder (4.8% vs. 0.3%) and kidney cancer (3.1% vs. 0.4%) when compared to those who did not.

Conclusion: Few patients complete a timely evaluation of MH. Women and underinsured patients are disproportionately less likely to complete a work-up for microhematuria and this may have downstream implications for diagnosis.

Keywords: Microhematuria; Hematuria; Bladder cancer; Kidney cancer; Cystoscopy

1. Introduction

Approximately 150,000 patients will be diagnosed with urothelial or kidney cancer each year in the United States. Unfortunately, survival for patients with genitourinary (GU) cancer is not equally stratified across genders and patients with varying insurance statuses [1]. Women and the underinsured are more likely to have higher stage incident disease, suggesting a delay in diagnosis [2,3]. For patients with GU cancer, the only early presenting symptom may be hematuria, either microscopic or gross. Early identification and evaluation of hematuria with urological consultation, diagnostic imaging and cystoscopy is associated with lower stage bladder cancer and improved survival [4,5].

A complete evaluation of microhematuria for most adults is currently recommend by multiple urological and primary care practice guidelines. However, the workup is

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complex and fragmented, requiring multiple referals and endoscopy from a surgical specialist [6,7]. Many patients do not complete this full evaluation and may be at risk of a missed or delayed identification of urinary tract pathology [8]. To date, the discrepancy between those patients found to have MH and those who ultimately complete a MH evaluation is poorly understood.

The goal of this study was to identify factors associated with patients completing a timely MH evaluation and conversely, those who did not. We hypothesized that female gender and worse insurance coverage was associated with noncompletion of the recommended MH evaluation. Using a unique electronic medical record-guided data warehouse, we were able to explore the specific clinical features, including urinalysis data, associated with a complete MH evaluation.

2. Materials and methods

2.1. Study design

We performed a retrospective cohort study of patients within our multi-institutional hospital system who were found to have microscopic hematuria. This study was approved by the Northwestern University IRB (Study STU00201732).

2.2. Patient cohort

Patients with a new diagnosis of microhematuria during the study period (August 1, 2007 to December 31, 2015) were included in the analysis. A new diagnosis of MH was defined as 3 or more red blood cells per high powered field (RBC/hpf) on a urinalysis (UA) in the absence of a benign cause [7,9]. Patients younger than 35 years of age were excluded in order to reflect the population currently recommended to undergo urologic evaluation by the AUA guidelines [7]. Only urinalyses collected during outpatient encounters were included to limit risk of instrumentation induced MH. Patients were excluded for benign cause if they were pregnant, had a concomitant urinary infection (defined as any positive or equivocal urine culture from the given urine sample), or had coexisting known medical renal disease as defined by documented International Classification of Disease Ninth Edition (ICD-9) diagnosis code. Patients with existing or prior diagnoses of urothelial cancer (bladder, 188.X; upper tract urothelial cancer (UTUC) 189.1-2), kidney cancer (189.X), prostate cancer (185.X), BPH (600.X), or urolithiasis (592.X and 594.X) were excluded. A "new diagnosis" was contingent on the patient having no prior diagnoses of hematuria (599.7x) and no prior urinalyses positive for hematuria (≥3 RBC/hpf) at any time in the electronic medical record before the study period. Patients with gross hematuria on index urinalysis were excluded by urinalysis color (pink or red) or by encounter ICD9 diagnosis code for gross hematuria (599.70, 599.71).

2.3. Data source

The Northwestern Medicine Enterprise Data Warehouse (EDW) is a medical system-wide data collection and integration platform. It is a continuously updated repository of more than 8 million unique patients that has been previously used for clinical research endeavors [10]. The EDW contains systematically extracted clinical data such as vital signs, lab values and physician entered information, diagnosis coding, and billing information. The data are sourced from multiple hospitals and outpatient clinical sites within the Northwestern Medicine healthcare system. There is a rigorous institutional quality assurance protocol in place. For this data set, approximately 1% of all charts had a confirmatory manual chart review to assure accuracy of the abstracted data.

2.4. Variables and outcomes

The primary outcomes of interest were the timing and completeness of the hematuria workup. Our primary dependent variable of interest was completion of a microhematuria workup which included both an appropriate imaging study and cystoscopy. Included imaging studies were any CT, MRI, or ultrasound test that could evaluate the GU organs and any cystoscopic CPT/ICD-9 procedure codes which evaluated the bladder and/or upper tracts (Supplement 1). Evaluation status for each patient was categorized in 1 of 3 ways: (a) "none/unknown" if there were no documented imaging studies or cystoscopic procedures, (b) "partial" or "incomplete" if either a cystoscopy or an imaging study was performed, and (c) "complete" if both were performed. Imaging studies and procedures completed outside of our healthcare system were not available or included. Additional outcomes of interest included percentage of patients diagnosed with bladder or kidney cancer and details regarding timing and completion of imaging and cystoscopy. GU malignancy diagnoses were determined from ICD-9 diagnosis codes. The percentage of patients with each diagnosis was assessed and stratified by a dichotomize evaluation status (complete vs. incomplete and none/unknown together).

Our primary independent variables of interest were gender and insurance status. Urinalysis microhematuria severity was included as a covariate and was categorized into 5 groups according to RBC/hpf: 0 to 2 (negative), 3 to 10, 11 to 50, 51 to 100, and >100. The subsequent urinalysis within 1 year after the index UA was also included as a "follow-up" urinalysis. Additional covariates included baseline demographic including age, race/ethnicity, and organ-system based comorbidities as categorized by the EDW via diagnosis code (Supplement 2). Race was categorized as White non-Hispanic, White Hispanic, Black, Asian, and other/unknown. Insurance status was derived according to documented payer as a 3-level variable: private insurance, Medicare/Medicaid, and uninsured/self-pay/other.

The time period was dichotomized as 2007 to 2011 and 2012 to 2015 to reflect changes in the AUA guidelines as of 2012, afterwhich a confirmatory second urinalysis for microhematuria was no longer required.

2.5. Statistical analysis

We performed bivariate analyses to test the association between the completeness of the microhematuria workup and all covariates. Continuous variables were compared using either the Mann-Whitney *U* test or Kruskal-Wallis test by ranks. Chi-squared analysis was used to compare proportions of categorical variables. We developed 2 multivariable adjusted binomial logistic regression models to determine the association between complete (yes/no) workup and age, gender, race, insurance status, and urinalysis data within 1 year and a complete evaluation at any time following the index urinalysis. All tests were designated to have significance at $P < 0.05$. All statistical analyses were completed using STATA version 13.

3. Results

3.1. Demographics

In total, 15,161 patients met inclusion criteria with a new diagnosis of MH in our hospital system over 7.5 years and were included in our cohort. There was a median follow-up time of 846 days (IQR 290−1743). In the entire cohort, the median age was 55 years old (IQR 46−65) and 69.2% of patients ($n = 10,477$) were women (Table 1). Significant unadjusted differences in the rates of completed microhematuria evaluations were seen between men (10.3%) vs. women (7.6%) as well as insured (9.0% and 10.0% for private and Medicare/Medicaid, respectively) vs. uninsured (4.3%) patients. The majority of patients presenting with a new diagnosis of MH had an index (first) UA with 3-10 RBC/hpf ($n = 11,098$, 73.3%). A higher percentage of patients with >100 RBC/hpf completed the full evaluation. Of all patients, 8,580 (56.5%) had a follow-up UA collected (Table 2). Median time between index UA and follow-up UA was 68 days [IQR 15−322 days].

3.2. Evaluation details

Overall, 22.8% (3,451) and 12.9% (1,948) of the entire cohort completed an imaging study and cystoscopy, respectively (Table 3). Median time to imaging study was 75 days (IQR 18−415 days) and cystoscopy 68.5 days (IQR 27−324.5 days). Of those with an imaging study, CT or MRI was performed in 95.9% (3,311) of patients while 4.1% (140) received an ultrasound. The complete evaluation cohort included 1,273 patients (8.4% of all patients), each of whom completed imaging and cystoscopy; only 899 (5.9% of all patients) completed both within 1 year of initial microscopic hematuria diagnosis. Of those with an incomplete evaluation, 23.7% underwent cystoscopy, and 76.3% underwent imaging.

Table 1
Demographic characteristics for all patients (column percentages) and for patients stratified by degree of microhematuria evaluation (row percentages), *P* value represents level of significance for chi-square test among the 3 strata of evaluation

		All ($n = 15,161$)	None/Unknown ($n = 11,035$)	Partial ($n = 2,853$)	Complete ($n = 1,273$)	*P* value
Age category	<50	5,497 (36.3)	4,182 (76.1)	883 (16.1)	432 (7.9)	<0.001
	50−59	3,886 (25.6)	2,775 (71.4)	759 (19.5)	352 (9.1)	
	60−69	3,140 (20.7)	2,136 (68.0)	688 (21.9)	316 (10.1)	
	70+	2,638 (17.4)	1,942 (73.6)	523 (19.8)	173 (6.6)	
Sex	Female	10,477 (69.2)	7,823 (74.7)	1,862 (17.8)	792 (7.6)	<0.001
	Male	4,669 (30.8)	3,197 (68.5)	991 (21.2)	481 (10.3)	
Race	White (NH)	7,717 (51.3)	5,534 (71.7)	1,519 (19.7)	664 (8.6)	<0.001
	White (H)	410 (2.7)	270 (65.9)	96 (23.4)	44 (10.7)	
	Black	2,525 (16.8)	1,826 (72.3)	480 (19.0)	219 (8.7)	
	Asian	445 (3.0)	320 (71.9)	76 (17.1)	49 (11.0)	
	Other/Unknown	3,940 (26.2)	2,970 (75.4)	676 (17.2)	294 (7.5)	
Insurance	Private insurance	7,946 (52.5)	5,812 (73.1)	1,418 (17.9)	716 (9.0)	<0.001
	Medicare/Medicaid	4,325 (28.6)	2,835 (65.6)	1,056 (24.4)	434 (10.0)	
	Self-pay/uninsured/unknown	2,861 (18.9)	2,360 (82.5)	378 (13.2)	123 (4.3)	
Comorbidities	Obesity	1,680 (11.1)	1,142 (68.0)	369 (22.0)	169 (10.1)	<0.001
	Heart disease	386 (2.6)	245 (63.5)	109 (28.2)	32 (8.3)	<0.001
	Hypertension	5,531 (36.5)	3,854 (69.7)	1,163 (21.0)	514 (9.3)	<0.001
	PVD	391 (2.6)	238 (60.9)	118 (30.2)	35 (8.9)	<0.001
	Liver disease	436 (2.9)	226 (51.8)	164 (37.6)	46 (10.6)	<0.001
	Pulmonary disease	2,256 (14.9)	1,458 (64.6)	568 (25.2)	230 (10.2)	<0.001
Time Period	2007−2010	7,273 (48.0)	4,808 (66.1)	1,662 (22.9)	803 (11.0)	<0.001
	2011−2015	7,888 (52.0)	6,227 (78.9)	1,191 (15.1)	470 (6.0)	

Table 2
Urinalysis data for all patients (column percentages) and for patients stratified by degree of microhematuria evaluation (row percentages), *P* value represents level of significance for chi-square test among the three strata of evaluation. Patients were considered to have "no follow-up" urinalysis if not completed within 12 months after initial urinalysis

		All (*n* = 15,161)	None/Unknown (*n* = 11,035)	Partial (*n* = 2,853)	Complete (*n* = 1,273)	*P* value
Index UA (RBC/hpf)	3−10	11,098 (73.3)	8,369 (75.4)	1,962 (17.7)	767 (6.9)	<0.001
	11−50	2,919 (19.3)	1,963 (67.3)	608 (20.8)	348 (11.9)	
	51−100	448 (3.0)	286 (63.8)	99 (22.1)	63 (14.1)	
	100+	685 (4.5)	407 (59.4)	183 (26.7)	95 (13.9)	
Follow-up UA (RBC/hpf)	0−2 (negative)	5,621 (37.1)	3,985 (70.9)	1,215 (21.6)	421 (7.5)	<0.001
	3−10	1,695 (11.2)	987 (58.2)	447 (26.4)	261 (15.4)	
	11−50	824 (5.4)	457 (55.5)	217 (26.3)	150 (18.2)	
	51−100	154 (1.0)	74 (48.1)	50 (32.5)	30 (19.5)	
	100+	286 (1.9)	123 (43.0)	88 (30.8)	75 (26.2)	
	No follow-up	6,581 (43.4)	5,409 (82.2)	836 (12.7)	336 (5.1)	

Table 3
Timing and percentages of patients with microhematuria completing either an imaging study, a cystoscopy, or both (considered a complete evaluation).

	Imaging	Cystoscopy	Complete evaluation
Completed (*n* = 15,161)	22.8% (3,451)	12.8% (1,948)	8.4% (1,273)
Median time to (days) [IQR]	75 [18−415]	68.5 [27−324.5]	104 [43−451]
Completed, as (%) of all patients			
Within 30 days	7.7% (1,165)	3.6% (545)	1.4% (213)
Within 180 days	14.3% (2,163)	8.9% (1,349)	5.1% (779)
Within 365 days	16.5% (2,506)	9.8% (1,489)	5.9% (899)
>365 days	6.2% (945)	3.0% (459)	2.5% (374)

3.3. Urologic cancer diagnoses

A total of 104 (0.7%) patients in our cohort were diagnosed with bladder cancer and 96 (0.6%) with kidney cancer/UTUC (Supplemental Table 1). There were significantly higher rates of both bladder (4.8% vs. 0.3%, $P < 0.01$) and kidney/UTUC (3.1% vs. 0.4%, $P < 0.01$) cancer in the complete evaluation cohort.

3.4. Factors associated with undergoing a complete evaluation

Female patients had lower odds of completing an evaluation for microhematuria at one year (odds ratio [OR] 0.72, 95% confidence interval [CI] 0.62−0.83) and at any time (OR 0.76, 95% CI 0.67−0.86) compared to men (Table 4). Patients with increasing severity (more RBC/hpf) of microhematuria on index UA were associated with increased odds of completing an evaluation at 1 year and any time after an initial diagnosis of microhematuria. Patients had lower odds of completing an evaluation at 1 year if they were older (OR 0.69, 95% CI 0.53−0.90) (70+ years old vs. <50 years old) or were uninsured/self-pay (OR 0.56, 95% CI 0.44−0.70; vs. private insurance).

4. Discussion

In this study, female gender and lack of insurance were associated with a lower odds of completing a timely microhematuria evaluation. This work further corroborates past studies that have also shown disparate rates of diagnostic evaluation and longer delays to evaluation for women [6,11−13]. Our findings may begin to explain why women are diagnosed at higher stages of urothelial malignancy and are more likely to die of their disease than their male counterparts [14]. This study further adds to these findings by demonstrating that severity of microhematuria on urinalysis (more RBCs/hpf) is independently related to completing an evaluation in both genders. Providers may be more concerned about patients with more RBC/hpf in urinalyses and this may lead to referral bias in presumably "higher risk" patients.

Additional characteristics associated with decreased likelihood of undergoing complete and timely evaluation include sources of payment outside of private insurance, particularly being uninsured or having to self-pay. Disparities in evaluation stemming from insurance coverage has been suggested in previous studies, as even privately insured patients bear a substantial proportion of the costs related to specialist consultations and diagnostics [6,15−17]. Thus, improving guideline adherence may need

Table 4
Binomial logistic regression model assessing covariates associated with completion of entire microhematuria evaluation (cystoscopy and upper tract imaging) within 1 year of MH diagnosis and at any time subsequent to MH diagnosis. Complete model presented with all included covariates.

	Evaluation within 1 year				Evaluation at any time			
	OR	95% CI lower/upper		*P* value	OR	95% CI lower/upper		*P* value
Age category								
<50	REF				REF			
50–59	1.12	0.94	1.34	0.2	1.14	0.98	1.32	0.1
60–69	1.17	0.97	1.43	0.1	1.16	0.98	1.37	0.09
70+	0.69	0.53	0.9	0.01	0.68	0.54	0.85	0.01
Sex								
Female	0.72	0.62	0.83	<0.01	0.76	0.67	0.86	<0.01
Male	REF				REF			
Race								
WNH	REF				REF			
WH	1.11	0.75	1.64	0.6	1.16	0.83	1.62	0.4
Black	0.85	0.7	1.04	0.11	0.94	0.8	1.11	0.48
Asian	1.19	0.81	1.73	0.37	1.4	1.01	1.92	0.04
Other	0.83	0.69	0.98	0.03	0.91	0.78	1.05	0.2
Insurance status								
Private insurance	REF				REF			
Medicare/Medicaid	1.03	0.86	1.25	0.73	1.15	0.98	1.34	0.09
Self pay/uninsured/unknown	0.56	0.44	0.7	<0.01	0.5	0.41	0.62	<0.01
Time period								
2007–2010	REF				REF			
2011–2015	0.77	0.67	0.89	<0.01	0.6	0.53	0.68	<0.01
Index UA (RBC/hpf)								
3–10	REF				REF			
11–50	1.74	1.48	2.04	<0.01	1.72	1.5	1.98	<0.01
50–100	2.11	1.53	2.93	<0.01	2.09	1.57	2.79	<0.01
100+	2.48	1.92	3.2	<0.01	2.03	1.6	2.58	<0.01
Follow-up UA category								
No f/u UA	REF				REF			
Negative	1.14	0.96	1.36	0.14	1.45	1.25	1.69	<0.01
Positive	3.05	2.58	3.61	<0.01	3.53	3.05	4.1	<0.01

to address logistic and financial barriers to care. Differences in odds of evaluation were seen even after adjusting for age in the Medicare population (>65 years old), further demonstrating that insurance status is an independent factor. Importantly, it is also possible that patients without insurance sought care elsewhere outside of our institution at public hospitals and were therefore not captured, thus biasing these results.

The decreased odds of completing a microhematuria evaluation in older patients is a finding unique to this study. This is especially concerning since age is a well known risk factor for GU malignancy. Current guidelines espouse a "1 size fits all" evaluation recommendation with poor supporting evidence. It is therefore conceivable that guideline recommendations to evaluate everyone with microhematuria and the infrequent incidence of malignant diagnoses has jaded providers from evaluating even high-risk individuals. Attempts to better risk stratify patients for evaluation in an evidence-based fashion are needed.

Similar to other prior studies, few patients (8.4% at all, 5.9% within 1 year) in our study were evaluated according to published urological guidelines, with most patients undergoing only partial evaluation. This adds to prior work by Ark et al. who assessed the variation in diagnostic evaluation among roughly 85,000 patients—most of whom were low income individuals from the South of the United States. They found similarly low rates of complete evaluation (18% within 180 days) and considerable variation in the degree of diagnostic work up among gender, race, and bladder cancer risk factors [18]. Interestingly, we found that among patients who only completed part of the work up, more had an imaging study (76.3%) than cystoscopy (23.7%). This may be due to anxiety about the invasiveness of the cystoscopy compared to the relative ease of the imaging study. Prior studies have shown differences in preprocedural anxiety among the genders and age and better patient education may improve adherence to the recommended cystoscopy [19].

As expected, the cohort of patients who were more completely evaluated had a higher incidence of GU malignancy. However, overall rates of malignancy in this study

were slightly lower than prior studies. This difference likely relates to the exclusion of patients with gross hematuria in our cohort. The generally low rate of malignancy seen in patients with microhematuria is an opportunity to focus diagnostic pursuits on those at highest risk. Over evaluation with invasive procedures and ionizing radiation may be harming our patients [20] at a significant cost to the health care system [21]; a change in the evaluation paradigm of microhematuria is needed.

This study is limited by a retrospective design, however the methods used allowed for a longer follow-up period. Our study includes a majority of female patients, which has been a weakness of prior publications. Given that men are epidemiologically more likely to have urinary tract malignancies, differences in referral patterns may reflect attempts at risk stratification at the primary physician level. This could also represent physician bias in over-attributing hematuria to benign causes commonly found in female patients such as urinary tract infection and menstruation. In these circumstances, repeat UA or UA following adequate treatment is important in distinguishing causal factors of microhematuria and truly confirming a benign cause [7].

Additionally, this study includes only patients from a single region associated with the Northwestern Medicine hospital system. While multiple sites and clinical settings (both community and academic hospitals as well as multiple outpatient primary and specialty clinics) within the Northwestern network were included and the sample size was large, it is possible that some patients may have gone outside of the health system for subsequent diagnostic care, resulting in underestimation of cystoscopy or imaging rates. Finally, the study is also limited somewhat by lack of smoking history and other exposures that may have influenced providers to complete varying degrees of evaluation according to risk stratification.

5. Conclusion

This study provides further evidence that few patients undergo complete microhematuria evaluation in accordance with current practice guidelines. Women and underinsured patients are disproportionately less likely to complete a diagnostic evaluation when presenting with microhematuria.

Conflict of interest

The authors declare no potential conflicts of interest.

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Supplementary materials

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