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Gender Disparities in Hematuria Evaluation and Bladder Cancer Diagnosis: A Population-Based Analysis

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Abstract

Purpose—Men are diagnosed with bladder cancer at three times the rate of women. However, women present with advanced disease and have poorer survival, suggesting delays in bladder cancer diagnosis. Hematuria is the presenting symptom in a majority of cases. Our objective was to assess gender differences in hematuria evaluation in older adults with bladder cancer.

Materials and Methods—Using the Surveillance, Epidemiology and End Results cancer registry linked with Medicare claims, we identified Medicare beneficiaries aged 66 years or older diagnosed with bladder cancer between 2000 and 2007 with a claim for hematuria in the year prior to diagnosis. We examined the impact of gender and demographic and clinical factors on time from initial hematuria claim to urology visit; and time from initial hematuria claim to hematuria evaluation including cystoscopy, upper urinary tract imaging, and urine cytology.

Results—Of 35,646 patients with a hematuria claim in the year preceding bladder cancer diagnosis, 97% had a urology visit claim. The mean time to urology visit was 27 days (range 0–377), and the time to urology visit was longer for women than for men (adjusted hazard ratio 0.9, 95% CI 0.87–0.92). Women were more likely to undergo delayed (after > 30 days) hematuria evaluation (adjusted odds ratio 1.13, 95% CI 1.07–1.21).

Conclusion—We observed longer time to a urology visit for women than for men presenting with hematuria. These findings may explain stage differences in bladder cancer diagnosis and inform efforts to reduce gender disparities in bladder cancer stage and outcomes.

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Keywords

access to care; bladder cancer; disparities; gender; quality of care

Background

Bladder cancer affected more than 70,000 Americans in 2012, and caused of almost 15,000 deaths.¹ Although men are diagnosed with bladder cancer at nearly three times the rate of women, women present with more advanced disease, and a greater proportion die of their disease.² Differences in stage distribution suggest that delayed diagnosis may explain at least some of the poorer outcomes observed in women.³⁻⁵

Over 80% of bladder cancers are diagnosed following the presenting symptom of hematuria.⁶ Hematuria is caused by benign and malignant conditions that vary by sex. In men, hematuria typically arises from a source in the urinary tract including kidney stones, bladder cancer, or kidney cancer. In women, hematuria may be attributed to urinary tract infections or gynecologic origins.

The American Urological Association (AUA) recommends a diagnostic workup of hematuria including cystoscopy, urine cytology, and upper urinary tract imaging.^{7,8} Any physician may order urine cytology and imaging; however, cystoscopy is performed almost exclusively by urologists. Despite clear guidelines for hematuria evaluation, women may be referred to urologists less often and after a longer time since first hematuria presentation than men.⁹ However, prior studies addressing this question have been limited in their scope, sample size and generalizability.⁹⁻¹¹

Our objectives were to estimate differences between men and women in the timeliness of hematuria evaluation and consultation with a urologist in a population-based cohort of older bladder cancer patients, and to identify predictors of delayed evaluation.

Methods

Data

We used Surveillance, Epidemiology and End Results (SEER) cancer registry data linked with Medicare claims. SEER is a consortium of population-based cancer registries in selected states and areas covering 30% of the US population.¹² SEER collects information regarding site and extent of disease, first course of cancer therapy, and date and cause of death. For adults age 65 and older diagnosed with cancer in SEER areas, cancer registry information is linked with Medicare claims for inpatient, outpatient and physician services. The SEER-Medicare files were used in accordance with a data-use agreement with the NCI. This study was reviewed by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center and deemed exempt research.

Cohort

We identified patients age 66 or older with a primary bladder cancer diagnosed between January 1, 2000 and December 31, 2007 and a claim for hematuria in the twelve months

prior to bladder cancer diagnosis. We included patients with known cancer stage and continuous enrollment in Medicare Parts A and B for at least one year prior to bladder cancer diagnosis. We excluded patients with prior malignancy and those enrolled in a Medicare managed care plan.

Outcomes

The primary outcome was time to first urology visit, defined as the interval between first Medicare claim for hematuria in the year prior to bladder cancer diagnosis and the first claim for a urologist visit. Urologists were identified by the Medicare Provider Specialty code.

A secondary outcome was time to initiation of hematuria evaluation, defined as the interval between first Medicare claim for hematuria in the year prior to bladder cancer diagnosis and first claim for cystoscopy, upper urinary tract imaging, or urine cytology. Upper tract imaging included computed tomography (CT) urogram, renal ultrasound, retrograde pyelogram, or intravenous pyelogram. Delayed hematuria evaluation was defined as an interval greater than 30 days between first hematuria claim and initiation of evaluation.

Covariates

The predictor of interest for each outcome was sex. In multivariable analysis we controlled for other characteristics including age, race, marital status, median income in the census tract of residence, urban vs. rural residence, comorbidity, geographic region, year of diagnosis, and specialty of the provider associated with the first claim for hematuria. Comorbidity was estimated using an adaptation of the Charlson comorbidity index based on claims in the year prior to bladder cancer diagnosis.¹³ Provider specialty associated with each patient's index hematuria claim was classified as primary care, obstetrics/gynecology, urology, or other. Primary care included internal medicine, family practice, general practice physicians, and nurse practitioners. Disease characteristics included bladder cancer stage, grade, histology, and lymph node involvement. Stage was classified according to the American Joint Committee on Cancer (AJCC) staging schema, 6th edition.¹⁴ To control for a pre-existing relationship with a urologist, we created a binary indicator reflecting the presence or absence of any Medicare claim for an encounter with a urologist preceding the index hematuria claim in the year prior to bladder cancer diagnosis.

Analysis

Unadjusted associations between sex and the frequency of each outcome (urology visit, cystoscopy, upper tract imaging, cytology) were assessed using chi-square tests. We estimated Kaplan-Meier survival functions and log-rank tests to assess unadjusted associations between sex and time to urology visit. We used Cox proportional hazards regression to estimate the impact of sex on time to first urology visit after the index hematuria claim, adjusting for demographic and disease characteristics. If the index hematuria claim coincided with a urology visit, the time to first urology visit was defined as a fraction of a day. Patients without a urology visit were censored at the time of bladder cancer diagnosis.

We used logistic regression to estimate the impact of sex on the likelihood of delayed hematuria evaluation, adjusting for demographic and disease characteristics. Observing a significant unadjusted association between specialty of the provider associated with the index hematuria claim and having a previous visit with a urologist, we included a single four-level variable reflecting the interaction of these two terms: specialty of the provider associated with index hematuria claim (urologist vs. other) and claim for urologist visit in the year prior to index hematuria claim (any vs. none). All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

We identified 41,229 bladder cancer patients, of whom 35,646 (86%) had at least one claim with a diagnosis of hematuria in the year prior to bladder cancer diagnosis. Of the 5370 excluded patients, 76% were male and 72% had a urology visit most commonly associated with codes for benign prostatic hyperplasia, urinary retention/incontinence/other, and bladder cancer. There were 26,119 men (73%) and 9,527 women (27%) who met our inclusion criteria for analysis. Compared with male patients, females were older, more likely to be black, less likely to be married, resided in more affluent areas, and had less comorbidity (Table 1). Women were more likely to have advanced-stage bladder cancer and lymph node involvement. Men were more likely to have a urologist associated with their index hematuria claim (32% vs. 24%), and they were more than twice as likely to have seen a urologist prior to hematuria diagnosis (29% vs. 13%).

Time to Urology Visit

The median time to first urology visit was 3 days, but varied by sex: 2 days for men and 6 days for women. The mean time to first urology visit was 27 days (range 0-377 days), but also varied by sex: 24 days for men and 35 days for women. In unadjusted comparison, women had slower times to urology visit (log-rank $p < 0.0001$, Figure 1). Controlling for demographic and disease characteristics, women were slower to see a urologist after their initial hematuria claim (adjusted hazard ratio 0.90, 95% CI 0.87-0.92, Table 2). Residence in a non-metropolitan area, in the Midwest or West, greater comorbidity, and high-grade cancer were also associated with a longer time to urology visit. Patients who had seen a urologist previously were quicker to see a urologist after hematuria diagnosis (adjusted HR 1.60, 95% CI 1.56-1.64).

Time to Hematuria Evaluation

The median time to initiation of hematuria evaluation for the entire cohort was 8 days (range 0-378 days). The median times were similar for men and women at 8 and 9 days, respectively. A claim for at least one component of hematuria evaluation was present in 87% of the cohort (Table 3). Men were slightly more likely than women to have cystoscopy at some point prior to cancer diagnosis (72% vs. 70%, $P < .001$). The first procedure marking initiation of hematuria evaluation was cystoscopy in 41% of the cohort, which was similar for men and women.

Of the 30,923 patients who had any component of hematuria evaluation, 7,941 (26%) experienced a delay of more than one month in initiation. Controlling for sociodemographic and disease characteristics, women were more likely to experience a delay than men (adjusted odds ratio 1.12, 95% CI 1.05-1.20, Table 4). Delayed evaluation was less likely among patients whose index hematuria claim was associated with a urologist (adjusted OR 0.26, 95% CI 0.24-0.29), who had seen a urologist in the year prior to hematuria diagnosis (adjusted OR 0.88, 95% CI 0.81-0.96) or both (adjusted OR 0.77, 95% CI 0.71-0.84). There was a trend toward greater odds of delay with more advanced tumor stage.

Discussion

In this large cohort of older bladder cancer patients, we found substantial gaps in the timeliness of hematuria evaluations. Initiation of hematuria evaluation was delayed by a month or longer in a quarter of all patients, and 13% of patients did not receive any component of a standard hematuria evaluation. We also found that women were slower to see a urologist following their initial presentation with hematuria.

Timely urologic consultation following a hematuria diagnosis is important for several reasons. First, cystoscopy is the only definitive test for visualizing bladder cancer, and it is performed exclusively by urologists. Second, most bladder cancers are initially treated with transurethral resection of the tumor, a surgical procedure performed almost exclusively by urologists.¹⁵ Timely urology referral, especially in older adults, may be considered a benchmark for quality of hematuria evaluation and bladder cancer management. Because urologists generally initiate bladder cancer treatment, a difference in first urology visit could contribute to poorer oncologic outcomes in women with bladder cancer.¹⁵ Similarly, several studies have documented poorer survival when the interval between confirmed bladder cancer diagnosis and definitive treatment exceeds three months.^{16, 17} Thus, we examined delayed evaluation as a secondary outcome, assuming that one month or longer between first presentation with hematuria to a physician and initiation of hematuria evaluation could result in overall treatment delays.

Our findings from a population-based cohort are consistent with prior studies of institution- and health plan-based cohorts and physician surveys. In one study of 1,500 patients with risk factors for bladder cancer and documented microscopic hematuria, 42% did not receive a hematuria evaluation consistent with guidelines.¹⁸ Among members of a large Midwestern health plan presenting with hematuria, only 27% of women were referred to a urologist, and women were referred more slowly than men.⁹ A survey of nearly 800 primary care physicians found that only 46% of physicians in Miami and 26% of physicians in Dallas referred patients with microscopic hematuria to a urologist, and not all patients with gross hematuria received a referral.¹⁰ These studies and ours raise concerns about systemic barriers to high-quality and timely hematuria evaluation, particularly for women.

Several factors might explain observed disparities in hematuria evaluation. Women may be erroneously treated for other diagnoses, such as urinary tract infections or postmenopausal bleeding, before being referred for further evaluation. In the large Midwestern health plan

study, women were more likely to be referred when they had recurring symptoms, while men were more likely to be referred after a single episode of hematuria.⁹

Women may take a more circuitous route through the healthcare system before seeing a urologist. Men may have an established relationship with a urologist, while women may see primary care or OB/GYN before seeing a urologist. In our cohort, men were more than twice as likely as women to have seen a urologist for any reason prior to hematuria diagnosis, and a previous encounter with a urologist was associated with more timely hematuria evaluation and earlier urology visit. In a recent survey of 200 newly diagnosed bladder cancer patients, 78% of men versus 55% of women reported that they initially consulted a urologist with their urinary symptoms. More women than men (16% vs. 4%) were treated for 3 or more urinary tract infections in the year prior to bladder cancer diagnosis.¹¹ While this may be a consequence of men having an established relationship with a urologist, it may also reflect biases toward less aggressive testing and treatment of women, as seen in studies of cardiac care.¹⁹ Even before seeing a health care provider, women may wait to seek medical attention, perhaps attributing symptoms to benign etiologies, or due to complacency from a lifetime of menstruation or prior urinary tract infections.²⁰ Investigation of the mechanisms for this disparity might inform targeted interventions to facilitate timely bladder cancer work-up and treatment in women.

Our study raises concerns about how hematuria evaluations are conducted and whether the care recommended under current guidelines is appropriate. Although few patients presenting with hematuria have bladder cancer, hematuria is the initial presenting symptom in more than 80% of bladder cancer cases.^{6, 21} Therefore, in the absence of effective screening for bladder cancer, the AUA currently recommends a thorough evaluation of persistent, asymptomatic, microscopic hematuria when benign urologic conditions have been ruled out.⁷ The costs and risks of invasive tests, such as cystoscopy, may be substantial.²² Thus, some experts have proposed a risk-stratified approach to hematuria evaluation, rather than subjecting all patients to all of the recommended diagnostic tests.²¹

Several limitations of our study should be noted. First, our study may not be applicable to privately insured patients and those younger than 66. Second, we had no information about smoking history, an important risk factor for bladder cancer. Smokers may have established relationships with healthcare professionals, receive closer monitoring for smoking-related illnesses, or be referred for symptom evaluation more quickly. Third, we defined the onset of hematuria by the presence of a Medicare claim with the relevant diagnosis code. If patients waited or experienced recurrent episodes of hematuria before seeking care, our analysis would underestimate the magnitude of delay.

Despite these limitations, our findings suggest that there are opportunities for improvement in the timeliness of hematuria evaluation in patients who are ultimately diagnosed with bladder cancer. Our results also suggest that women are susceptible to delays in referral to a urologist, and are at greater risk of delayed hematuria evaluation. These findings raise questions about systemic forces underlying gender disparities, particularly for urology visits. Further investigation may better elucidate the mechanisms for observed sex differences in hematuria evaluation. At the very least, educational interventions regarding urologic health

for women, and quality improvement programs for providers and health systems, could begin to close the gender gap in hematuria evaluation, hopefully reducing disparities in bladder cancer survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key of Abbreviations

AUA	American Urological Association
SEER	Surveillance, Epidemiology and End Results
CT	computed tomography
OB/GYN	obstetrics/gynecology
AJCC	American Joint Committee on Cancer

Figure 1. Time to Urology Visit By Sex

Table 1

Characteristics of the Cohort By Sex

	All patients		Female		Male		P Value ^a
	No. Pts	%	No. Pts	%	No. Pts	%	
Age at diagnosis	35,646	–	9,527	27	26,119	73	–
66-69	5,062	14	1,225	13	3,837	15	<.001
70-74	7,811	22	1,839	19	5,972	23	
75-79	8,895	25	2,245	24	6,650	25	
80-84	7,575	21	2,107	22	5,468	21	
85	6,303	18	2,111	22	4,192	16	
Race/ethnicity							<.001
White	32,750	92	8,497	89	24,253	93	
Black	1,361	4	611	6	750	3	
Hispanic	430	1	117	1	313	1	
Asian	641	2	158	2	483	2	
Other	464	1	144	2	320	1	
Married							<.001
Yes	21,176	59	3,119	33	18,057	69	
No/unknown	14,470	41	6,408	67	8,062	31	
Median income							<.01
1st quartile	8,904	25	2,502	26	6,402	25	
2nd quartile	8,918	25	2,355	25	6,563	25	
3rd quartile	8,907	25	2,385	25	6,522	25	
4th quartile	8,917	25	2,285	24	6,632	25	
Urban-rural residence							<.001
Metropolitan	30,088	84	8,147	86	21,941	84	
Non-metropolitan	5,558	16	1,380	14	4,178	16	
Region							<.001

	All patients		Female		Male		P Value ^a
	No. Pts	%	No. Pts	%	No. Pts	%	
	35,646	-	9,527	27	26,119	73	-
Northeast	9,916	28	2,850	30	7,066	27	
South	6,286	18	1,673	18	4,613	18	
Midwest	4,882	14	1,350	14	3,532	14	
West	14,562	41	3,654	38	10,908	42	
Charlson comorbidity score							
0	19,888	56	5,630	59	14,258	55	<.001
1	9,099	26	2,357	25	6,742	26	
2	6,659	19	1,540	16	5,119	20	
Tumor stage							
I	26,807	75	6,760	71	20,047	77	<.001
II	5,797	16	1,782	19	4,015	15	
III	2,440	7	726	8	1,714	7	
IV	273	1	133	1	140	1	
Unknown	329	1	126	1	203	1	
Lymph node involvement							
No	32,370	91	8,542	90	23,828	91	<.001
Yes	965	3	324	3	641	2	
Unknown	2,311	6	661	7	1,650	6	
Histology							
Urothelial	35,174	99	9,319	98	25,855	99	<.001
Squamous cell	313	1	153	2	160	1	
Adenocarcinoma	159	<1	55	1	104	<1	
Tumor grade							
Low	16,083	45	4,379	46	11,704	45	<.05
High	17,109	48	4,535	48	12,574	48	
Unknown	2,454	7	613	6	1,841	7	

	All patients		Female		Male		P Value ^a
	No. Pts	%	No. Pts	%	No. Pts	%	
Physician specialty ^b	35,646	–	9,527	27	26,119	73	–
Primary care	10,132	28	2,893	30	7,239	28	<.001
OB/GYN	189	1	189	2	0	--	
Urologist	10,697	30	2,297	24	8,400	32	
Other	11,230	32	3,101	33	8,129	31	
Missing	3,398	10	1,047	11	2,351	9	
Prior visit with urologist ^c							<.001
Yes	8,781	25	1,221	13	7,560	29	
No	26,865	75	8,306	87	18,559	71	

^a P-value for chi-square test of association between patient sex and each characteristic.

^b Specialty of the physician associated with initial claim for hematuria.

^c Encounter with urologist in the year prior to initial claim for hematuria.

Abbreviations: NS, non-significant; OB/GYN, obstetrician/gynecologist.

Table 2
Predictors of Time to First Urology Visit After Initial Hematuria Claim

	HR	(95% CI)	P Value^a
Age at diagnosis, y			NS
66-69	Ref		
70-74	1.03	(1.00-1.07)	
75-79	1.04	(1.01-1.08)	
80-84	1.03	(1.00-1.07)	
85	1.02	(0.99-1.06)	
Sex			<.001
Male	Ref		
Female	0.90	(0.87-0.92)	
Race/ethnicity			NS
White	Ref		
Black	0.93	(0.87-0.98)	
Hispanic	0.97	(0.88-1.08)	
Asian	0.98	(0.90-1.06)	
Other	0.97	(0.88-1.06)	
Married			<.001
No/unknown	Ref		
Yes	1.06	(1.04-1.09)	
Median income			0.001
1st quartile	Ref		
2nd quartile	1.01	(0.98-1.04)	
3rd quartile	1.03	(0.99-1.06)	
4th quartile	1.07	(1.03-1.10)	
Urban-rural residence			<.001
Metropolitan	Ref		
Non-metropolitan	0.91	(0.88-0.94)	
Region			<.001
Northeast	Ref		
South	1.04	(1.00-1.08)	
Midwest	0.92	(0.89-0.96)	
West	0.85	(0.83-0.87)	
Charlson comorbidity score			<.001
0	Ref		
1	0.96	(0.94-0.99)	
2	0.93	(0.90-0.95)	

	HR	(95% CI)	P Value ^a
Tumor stage			NS
I	Ref		
II	0.98	(0.95-1.01)	
III	1.02	(0.98-1.07)	
IV	1.04	(0.91-1.17)	
Lymph node involvement			NS
No	Ref		
Yes	1.04	(0.96-1.12)	
Unknown	0.99	(0.95-1.03)	
Histology			<.001
Urothelial	Ref		
Squamous cell	1.27	(1.13-1.42)	
Adenocarcinoma	0.83	(0.70-0.98)	
Tumor grade			<.05
Low	Ref		
High	0.97	(0.95-0.99)	
Unknown	1.00	(0.95-1.04)	
Prior visit with urologist ^b			<.001
No	Ref		
Yes	1.60	(1.56-1.64)	

^a P-value for adjusted association between characteristic and time to urology visit.

^b Encounter with urologist in the year prior to initial claim for hematuria.

Abbreviations: HR, hazard ratio; CI, confidence interval; NS, non-significant.

Table 3
Components of Hematuria Evaluation

	All patients	Female	Male	P Value^a
	No. Pts (%)	No. Pts (%)	No. Pts (%)	
	35,646	9,527	26,119	
Urology visit	34,482 (97)	9,206 (97)	25,276 (97)	NS
Hematuria evaluation ^b	30,923 (87)	8,264 (87)	22,659 (87)	NS
Cystoscopy				
1st test	12,574 (41)	3,306 (40)	9,268 (41)	NS
Ever	22,156 (72)	5,787 (70)	16,369 (72)	<.001
Upper urinary tract imaging ^c				
1st test	10,909 (35)	2,917 (35)	7,992 (35)	NS
Ever	18,741 (61)	5,028 (61)	13,713 (61)	NS
Urine cytology				
1st test	7,440 (24)	2,041 (25)	5,399 (24)	NS
Ever	12,558 (41)	3,462 (42)	9,096 (40)	<.01

^aP-value for chi-square test of association between patient sex and receipt of the specified service.

^bIf tests were done on the same day, this hierarchy was applied to determine the “first test”: cystoscopy, imaging, cytology.

^cUpper urinary tract imaging includes at least one of the following: computed tomography (CT) urogram, renal ultrasound, retrograde pyelogram, or intravenous pyelogram.

Abbreviations: NS, non-significant.

Table 4
Predictors of Delay of Hematuria Evaluation

	OR	(95% CI)	P Value
Age at diagnosis, y			<.001
66-69	Ref		
70-74	0.93	(0.85-1.02)	
75-79	0.96	(0.88-1.05)	
80-84	1.04	(0.95-1.14)	
85	1.11	(1.01-1.22)	
Sex			<.001
Male	Ref		
Female	1.12	(1.05-1.20)	
Race/ethnicity			NS
White	Ref		
Black	1.11	(0.97-1.28)	
Hispanic	0.96	(0.75-1.22)	
Asian	1.16	(0.96-1.40)	
Other	1.12	(0.90-1.40)	
Married			<.001
No/unknown	Ref		
Yes	0.89	(0.84-0.94)	
Median income			NS
1st quartile	Ref		
2nd quartile	0.99	(0.91-1.07)	
3rd quartile	0.92	(0.84-1.00)	
4th quartile	0.92	(0.85-1.00)	
Urban-rural residence			NS
Metropolitan	Ref		
Non-metropolitan	1.04	(0.96-1.13)	
Region			<.001
Northeast	Ref		
South	0.96	(0.87-1.04)	
Midwest	0.91	(0.83-1.00)	
West	1.15	(1.07-1.23)	
Charlson comorbidity score			<.001
0	Ref		
1	1.10	(1.04-1.18)	
2	1.29	(1.21-1.39)	

	OR	(95% CI)	P Value
Tumor stage			NS
I	Ref		
II	1.06	(0.98-1.14)	
III	1.08	(0.96-1.21)	
IV	1.18	(0.88-1.59)	
Lymph node involvement			NS
No	Ref		
Yes	0.96	(0.80-1.15)	
Unknown	0.96	(0.86-1.08)	
Histology			<.01
Urothelial	Ref		
Squamous cell	0.72	(0.53-1.00)	
Adenocarcinoma	1.55	(1.07-2.24)	
Tumor grade			NS
Low	Ref		
High	1.06	(1.00-1.13)	
Unknown	1.03	(0.93-1.15)	
Physician specialty ^a			<.001
Primary care	Ref		
OB/GYN	1.03	(0.75-1.43)	
Urologist	0.34	(0.31-0.68)	
Other	0.63	(0.59-0.68)	
Missing	0.95	(0.87-1.04)	
Prior visit with urologist ^b			<.001
No	Ref		
Yes	0.73	(0.68-0.78)	

^a Specialty of the physician associated with initial claim for hematuria.

^b Encounter with urologist in the year prior to initial claim for hematuria.

Abbreviations: OR, odds ratio; CI, confidence interval; NS, non-significant; OB/GYN, obstetrician/gynecologist.