Prospective External Validation of a Bladder Cancer Detection Model

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Purpose: Few studies have combined clinical prognostic factors with urinary biomarkers into risk profiles that can be used to predict the likelihood of bladder cancer. We previously developed and internally validated a bladder cancer detection nomogram that combines clinical features with the NMP22® BladderChek® test. To consider extensive use of the model the nomogram was tested in a prospective cohort of patients who presented with hematuria.

Materials and Methods: Patients referred for hematuria evaluation were prospectively enrolled at 3 centers. Each patient underwent complete urological evaluation, including history, examination, cystoscopy, cytology and NMP22. A logistic regression model to predict urothelial bladder carcinoma was also developed to compare the performance of clinical data with and without adding NMP22 and urinary cytology.

Results: The study included 381 patients (50.7% women) with a median age of 58 years. Urothelial bladder carcinoma was detected in 23 patients (6%). It was associated with age greater than 65 (11.1% vs 4% of patients, $p = 0.012$), male gender (10.1% vs 2%, $p = 0.003$), white ethnicity (9.2% vs 3.1%, $p = 0.016$), gross hematuria (9.9% vs 2.5%, $p = 0.005$), positive NMP22 (37% vs 3.7%, $p < 0.001$) and positive cytology (83.3% vs 3.9%, $p < 0.001$). Predictive accuracy of the bladder cancer detection nomogram was 80.2%. The calibration plot indicated that the previously published nomogram was well calibrated in patients with a less than 15% predicted probability of urothelial bladder carcinoma.

Conclusions: We prospectively validated a highly accurate tool that combines clinical factors and a urinary biomarker to detect bladder cancer. This tool can help prioritize urological referrals for patients with hematuria.

Key Words: urinary bladder, urinary bladder neoplasms, nuclear matrix protein 22, hematuria, prognosis

Abbreviations and Acronyms

BC = bladder cancer

FDA = Food and Drug Administration

UCB = urothelial bladder carcinoma

Accepted for publication May 13, 2014.

Study received approval from the institutional review board for the protection of human subjects.

Supported by Alere.

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† Financial interest and/or other relationship with Alere, Metabolon, Pacific Edge, Abbott and Cepheid.

An estimated 72,570 new cases of BC and 15,210 deaths from BC were expected in 2013 in the United States.[1] Of the new cases 54,610 and 17,960 were estimated to occur in men and women, respectively. Risk factors for UCB are well known, including older age, tobacco use and chemical exposure.[2] One of the most significant problems when treating UCB is that 25% of patients with UCB are diagnosed with muscle invasive disease, which has a significant impact on mortality compared to

0022-5347/14/1925-1343/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.05.087
Vol. 192, 1343-1348, November 2014
Printed in U.S.A.

that in patients diagnosed with noninvasive disease.[3,4] In fact, most advanced BC cases are diagnosed at that stage.

Currently UCB is primarily diagnosed after patients become symptomatic with blood in the urine that is visible (gross) or microscopic. While the risk of malignancy is approximately 10% in patients with gross hematuria, it is considerably lower in patients with microscopic hematuria.[5–7] The AUA (American Urological Association) best practice policy recommends cystoscopy for all adults older than 35 years with microscopic hematuria, defined as 3 red blood cells or greater per high power field.[8] However, this policy results in invasive evaluation with cystoscopy and imaging in 95% of patients with microscopic hematuria without any malignancy identified. The problem that clinicians face is that 9% to 18% of apparently normal individuals have some degree of hematuria.[5,9,10] Furthermore, the positive predictive value for detecting UCB by dipstick testing and in studies in which patients with microscopic hematuria were evaluated is low at 2% to 5%.[5,11] As such, clinicians must decide whether to send each patient with microhematuria to be evaluated for UCB.

Unfortunately recent studies showed that most patients with microscopic hematuria are not referred for evaluation by a urologist and do not undergo imaging or cystoscopy.[12–15] Due to this problem of inconsistent referrals a delayed diagnosis of UCB is common, leading to a worse prognosis as the result of more advanced stage at diagnosis.[16] Notably a greater proportion of women with UCB die of the disease, likely secondary to delayed diagnosis.[17] Therefore, UCB should be detected at its earliest and most localized stage, when it can be effectively controlled. The challenge for clinicians is to determine which patients are at greatest risk for UCB so that early referral and diagnosis can be done.

A large number of urinary biomarkers have been developed to detect BC. However, the performance of these biomarkers has been addressed without considering routine clinical prognostic features such as patient age, gender, smoking history and the presence or absence of hematuria.[7,18] We addressed this void by developing a nomogram that combines routine clinical features with the NMP22 BladderChek test, a point of care assay that detects the urine level of NMP22 protein and is FDA approved for UCB diagnosis.[19,20] This nomogram was developed and internally validated using split sampling in a large cohort of patients who presented with risk factors for BC.[19]

The main goal of the current study was to externally validate the UCB detection nomogram in a prospective, multicenter cohort using clinical factors, urine cytology and the NMP22 test.

MATERIALS AND METHODS

All procedures described in the current study were performed with the approval and oversight of the institutional review board for the protection of human subjects.

Objective and Locations

The primary study objective was to validate a BC detection nomogram based on clinical factors, urine cytology and the NMP22 test. The study was done at University of Texas Southwestern Medical Center at Dallas, University of Texas Health Science Center at San Antonio and Weill Cornell Medical College, New York Presbyterian Hospital in New York. Patients were prospectively enrolled at University of Texas Southwestern Medical Center at Dallas between December 2009 and March 2013. Enrollment at University of Texas Health Science Center at San Antonio was done from June 2011 to March 2013. Enrollment at Weill Cornell Medical College was done from April 2011 to February 2013.

Design

We prospectively enrolled patients referred to the urology clinic with a history of or presenting with gross or microscopic hematuria. Each individual who met enrollment criteria as described underwent hematuria evaluation, including cystoscopy, cytology, NMP22 and upper tract imaging. Clinical information was collected on each patient along with evaluation results. Ethnicity was assessed due to known differences in UCB incidence. Ethnicity was self-classified by participants from the options white, black, Hispanic, Asian and other. Cytology was considered positive when reported as malignant or suspicious cells. All other findings were deemed benign. Smoking was categorized as never, ever or current. The WHO 2004 classification was used to categorize biopsies for histology. Figure 1 shows a flow diagram of study procedures.

NMP22 BladderChek Test Device

The NMP22 BladderChek test is a FDA approved, point of care, lateral flow immunochromatographic qualitative assay. It detects increased amounts of the nuclear mitotic apparatus protein, a component of the nuclear matrix that is essential for cell division that is released in urine during cell death.[19] The assay is performed by adding 4 drops of voided urine to the sample well of the device. Results are read visually 30 to 50 minutes later in the test window. A built-in control indicates that the test is performing properly.

Patient Eligibility

Study inclusion criteria were that the subject 1) presented with or had a history of gross (visible) or microscopic hematuria, defined as 3 red blood cells or greater per high power field, and 2) was willing and able to provide written informed consent. Exclusion criteria were that the subject 1) had an active urinary tract infection, urinary retention, stone disease (renal or bladder), kidney failure, ureteral stents, nephrostomy tubes, bowel interposition or recent genitourinary instrumentation within 10 days, 2) had a history of genitourinary cancer, 3) was previously evaluated for BC, 4) had active