BC is an important malignancy from the epidemiological, socio-economic and clinical perspective. Currently screening is not recommended, and most patients are diagnosed after presenting with hematuria to their clinician. Delays in diagnosis are common and lead to a worse prognosis as a result of a more advanced stage at diagnosis (Wallace DM, Bryan RT, Dunn JA, Begum G, Bathers S. Delay and survival in bladder cancer. BJU Int 2002; 89: 868–78).

It is obvious that patients with macrohematuria need evaluation, but it is more difficult to individualize care for patients with microhematuria.

The use of algorithms and nomograms combining genotypic and phenotypic variables to detect bladder cancer in patients who present with microhematuria has been frequently reported. There is a potential of a non-invasive, relatively inexpensive screening test for a serious lethal disease that can be obtained in the office or clinic setting without exposing the patient to the risks of invasive procedures or radiation and contrast exposure. Another advantage of these algorithms is the ability for further optimization of the approach to patients with asymptomatic hematuria in regard not only to reduce patient concern, but also to a more consistently and effectively use of health care resources.

- Major Compulsory Revisions

1. Methods-Patient selection, 1st Paragraph

There is not a clear picture if there was an evaluation of the upper urinary tract included in the diagnostic work up of the study group. If yes, which were exactly the diagnostic tools?

Although the prevalence of the upper urinary tract urothelial carcinoma is small, an evaluation of the upper and lower urinary tract is required. (Carmack AJ, Soloway MS: The diagnosis and staging of bladder cancer: from RBCs to TURs. Urology 67 (3 Suppl 1): 3-8; discussion 8-10, 2006.)

CT urography is the imaging procedure of choice in the evaluation of microscopic hematuria because of its high sensitivity (91% to 100%) and specificity (94% to 97%), and its ability to provide excellent diagnostic information in a single imaging session.


2. Results-Sample demographics, 2nd Paragraph

There is not an unambiguous picture about the performance-sensitivity of these algorithms low grade cancer and what was the distribution of these cancers in your study. 60% of urothelial tumors at presentation are low grade and stage lesions (Messing EM, Young TB, Hunt VB, et al.: Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. Urology 1995, 45:387.) Unfortunately, it cannot be stated that the omission of low-grade tumours has no consequences. Those lesions might progress in grade and/or stage if left untreated. In case of low sensitivity for the latter cancers, they cannot be used to decide which patient with microhematuria can safely forgo cystoscopy.

- Discretionary Revisions

1. Methods-Patient selection, 1st Paragraph

-The duration of follow up was relatively small. Although bladder cancer is almost never incidentally found at autopsy, because it’s preclinical duration is probably brief, the duration of follow-up in the present study, stands not of considerable length. The brief duration of follow-up in the screened group may have artifically improved the outcome. (See also AUA Guidelines-although “Expert’s Opinion”: “…For persistent or recurrent asymptomatic microhematuria after initial negative urologic work-up, repeat evaluation within three to five years should be considered”… “If a patient with a history of persistent asymptomatic microhematuria has two consecutive negative annual urinalyses (one per year for two years from the time of initial evaluation or beyond), then no further urinalyses for the purpose of evaluation of AMH are necessary”)

Madeb et al have showed, that if appropriate workup does not reveal nephrologic or urologic disease, then annual urinalysis should be performed for at least two years after initial referral.

-Madeb R, Golijanin D, Knopf J, et al. Long-term outcome of patients with a
If these two urinalyses do not show persistent hematuria, the risk of future malignancy is less than 1%, and the patient may be released from care.
The probability of missing malignant disease overall was 1.7% (95% CI, 0.95-3.04) but this rose sharply to >4% for males over 60 with macroscopic haematuria.
Appropriate follow-up for patients with hematuria may require reconsideration in light of all these data.

2. Methods-Patient selection, last sentence
“Ethical approval for this study was granted by all participating centers and informed consent obtained from all patients providing samples”:
Please add approval number if that is according to publisher guidelines

3. Methods-Statistical analysis, 1st Paragraph
Quantification of tobacco use could have improved the accuracy of your model. Furthermore, addition of additional risk factors and occupational or other chemical exposures would likely also improve the model’s predictive accuracy. The truth is that very few patients present with significant exposures. However, a hypothetical >60-year old male patient with a history of smoking who presents with microscopic hematuria and even negative urine cytology has approximately a 17.5% chance of having bladder cancer. (Silverman DT, Levin LI, Hoover RN, Hartge P. Occupational risks of bladder cancer in the United States: I. White men. J Natl Cancer Inst. 1989;81:1472–1480.)

4. Discussion, 5th Paragraph
The application of the studied indexes should not be examined as an alternative to the use of urine cytology, even when used in a primary evaluation setting, but as an alternative to cystoscopy. Voided urine cytology is less sensitive than cystoscopy in the detection of bladder cancer (48% vs. 87%) (Cohen RA, Brown RS. Clinical practice. Microscopic hematuria. N Engl J Med. 2003;348(23):2330–2338.) and the AUA guideline no longer recommends it as part of the routine evaluation of microscopic hematuria (Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. American Urological Association Education and Research, Inc., 2012:1–30.).
It is considerable that even in patients who are taking anticoagulants, asymptomatic microscopic hematuria also requires urologic and nephrologic evaluation, regardless of the type or level of anticoagulant therapy.


We hope that use of indexes and algorithms, if established, will result in increased and earlier referrals of patients with hematuria to urologists, as it may help illustrate the non-trivial risk of having bladder cancer, even for patients with minimal risk factors. This might improve patient care through earlier diagnosis resulting in more timely treatment.

There are studies in which patients with hematuria rarely underwent complete evaluation. Although established risk factors for malignancy were associated with increasing use of diagnostic testing, factors unassociated with risk, such as practice site, also accounted for significant variation. (Am J Med. 2014 Jul;127(7):633-640.e11. doi: 10.1016/j.amjmed.2014.01.010. Epub 2014 Jan 28. Variation in the intensity of hematuria evaluation: a target for primary care quality improvement. Friedlander DF, Resnick MJ, You C, Bassett J, Yarlagadda V, Penson DF, Barocas DA)

Additionally, in the workup of hematuria, a urologist is needed not only to rule out the presence or absence of urinary tract malignancy. Stones, inflammatory and infectious lesions, benign prostatic hyperplasia or malignancy and vascular malformations may all result in blood in the urine. Therefore, while understanding the fact that cancer is not the only reason for a urologist to evaluate hematuria, it is a rational belief to assume that future guidelines could be revised so that fewer patients would need to be aimlessly evaluated.

The future of model development which incorporating both genotypic and phenotypic variables seems bright. New techniques are emerging and beyond finding good markers, the financial cost–effectiveness will be an important issue and that has not been studied sufficiently yet. Currently, no single model can guide us also in surveillance and lower the frequency of urethrocystoscopy. Whether use of a set of markers will be the answer will have to be studied.

Level of interest:An article whose findings are important to those with closely related research interests

Quality of written English:Acceptable

Statistical review:Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

I declare that I have no competing interests