RESEARCH ARTICLE

Stratifying Patients with Haematuria into High or Low Risk Groups for Bladder Cancer: a Novel Clinical Scoring System

Guan Hee Tan[1]*, Shamsul Azhar Shah[2], Ho Sue Ann[3], Siti Nurhafizah Hemdan[3], Lim Chun Shen[3], Nurudin Al-Fahmi Abdul Galib[3], Praveen Singam[1], Christopher Ho Chee Kong[1], Goh Eng Hong[1], Badrulhisham Bahadzor[1], Zulkifli Md Zainuddin[1]

Abstract

Haematuria is a common presentation of bladder cancer and requires a full urologic evaluation. This study aimed to develop a scoring system capable of stratifying patients with haematuria into high or low risk groups for having bladder cancer to help clinicians decide which patients need more urgent assessment. This cross-sectional study included all adult patients referred for haematuria and subsequently undergoing full urological evaluation in the years 2001 to 2011. Risk factors with strong association with bladder cancer in the study population were used to design the scoring system. Accuracy was determined by the area under the receiver operating characteristic (ROC) curve. A total of 325 patients with haematuria were included, out of which 70 (21.5%) were diagnosed to have bladder cancer. Significant risk factors associated with bladder cancer were male gender, a history of cigarette smoking and the presence of gross haematuria. A scoring system using 4 clinical parameters as variables was created. The scores ranged between 6 to 14, and a score of 10 and above indicated high risk for having bladder cancer. It was found to have good accuracy with an area under the ROC curve of 80.4%, while the sensitivity and specificity were 90.0% and 55.7%, respectively. The scoring system designed in this study has the potential to help clinicians stratify patients who present with haematuria into high or low risk for having bladder cancer. This will enable high-risk patients to undergo urologic assessment earlier.

Keywords: Haematuria - bladder cancer - scoring system - risk stratification - nomogram

Asian Pac J Cancer Prev, **14 (11)**, 6327-6330

Introduction

Haematuria is a common presentation of bladder cancer (Messing, 2007; Madeb and Messing, 2008). As such, patients with haematuria should be assessed thoroughly for the presence of this malignancy. A full urologic assessment of a patient with haematuria includes repeated urinalysis, urine culture, upper urinary tract imaging, cystoscopic examination (CE) and urinary cytology (Grossfeld et al., 2001). CE requires specialized endoscopic equipment and a well-trained team of medical personnels to perform it effectively and efficiently. It remains the most reliable method to assess the bladder for cancer (Grossfeld et al., 2001; Messing, 2007). To date, there is no single test that can replace the list of investigations that a patient with haematuria has to go through. Neither is there a method that can safely exclude the presence of bladder cancer in a patient with haematuria, without the use of CE (Khadra et al., 2000; Grossfeld et al., 2001; Messing, 2007; Lotan et al., 2009).

Delays in the treatment of bladder cancer have been shown to be detrimental to the survival outcome (Wallace et al., 2002; Gore et al., 2009). Bearing in mind that bladder cancer survival is significantly better when detected and treated at an early stage, this usually compels us to perform the investigations as soon as possible (Grossman et al., 2005; Messing, 2007; Madeb and Messing, 2008). This compulsion places a substantial burden on the urology units because of the need for CE. It also means that certain patients who really harbour bladder cancer could be diagnosed later simply because they did not receive an early assessment. Therefore, it would be useful to identify the patients with haematuria who are at a higher risk of having bladder cancer. This group of patients can then be assessed earlier and hopefully improve the detection rate of early stage bladder cancer. The aim of this study was to develop a scoring system to stratify patients with haematuria into high or low risk for having bladder cancer.

Materials and Methods

This was a cross-sectional study of all adult patients who were referred to the Urology Unit of Universiti

*[1]Urology Unit, Department of Surgery, [2]Department of Community Health, [3]Department of Surgery, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia *For correspondence: guanhee3479@yahoo.com*

Kebangsaan Malaysia Medical Centre for haematuria from the year 2001-2011. Only patients who had full urologic assessment for haematuria were included (Grossfeld et al., 2001). The patients with incomplete data of their assessment or had bladder cancer diagnosed outside of the study period were excluded. The patients were chosen from the Urology Unit database and their data were collected from the hospital records. Data on patient demography and the presence of common risk factors for bladder cancer in each of them were recorded. The variables that were taken into account were age, gender, presence of gross haematuria, and history of smoking and urinary tract infections (UTI).

The data was analyzed using IBM SPSS software version 20. Univariate analysis was performed to determine the association each of these risk factors have with bladder cancer within this study population. A scoring system was designed by including variables that were significantly associated with bladder cancer. Each of these symptoms was given a score according to the magnitude of their association with bladder cancer. This meant that, the greater the odds ratio obtained for the variable, the larger the score assigned to it in the scoring system. The accuracy of the scoring system was determined by the area under the receiver operating characteristic (ROC) curve. The most suitable cut-off point was decided. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

This study was carried out after obtaining approval from the Research and Ethics Committee of Universiti Kebangsaan Malaysia.

Results

Between the years 2001 and 2011, 405 cases of haematuria were referred the Urology Unit for further management. Out of these, 325 cases were included while 80 cases were excluded from the study due to incomplete data. In this period, 70 (21.5%) out of 325 patients who were investigated for haematuria were diagnosed to have bladder cancer. Patients of Chinese descent accounted for most of the bladder cancer cases (58.6%). This was followed by patients of Malay and Indian ancestries, accounting for 37.1% and 4.3% of bladder cancer cases respectively.

The average age of patients in the bladder cancer group was 62.5±11.4 years. This was slightly older than the patients who did not have bladder cancer, whose average age was 60.3±13.5 (p=0.207). It was found that male patients who had haematuria were at a greater risk of having bladder cancer (OR=2.04, 95%CI:1.14-3.64). Smokers or ex-smokers with haematuria were also noted to be more at risk of bladder cancer compared to non-smokers (OR=4.77, 95%CI:2.73-8.34). This study included patients with either microscopic or gross haematuria. When this was analyzed, there were significantly more patients with gross haematuria in the bladder cancer group. The odds ratio of patients with gross haematuria having bladder cancer over those with microscopic haematuria was 15.74, 95%CI:6.57-37.70.

A history of having UTI did not seem to increase the probability of having bladder cancer among patients with haematuria. Among those who had bladder cancer, 7.1% of them had a history of UTI. The proportion of patients who had a history of UTI in the non-bladder cancer group was 13.3% (p=0.158).

Table 1. The Scoring System for Stratifying Patients with Haematuria into High or Normal Risk for Bladder Cancer

Clinical factor		Points
Age (years)	≥50	2
	<50	1
Gender	Male	2
	Female	1
Smoking status	Smoker/ex-smoker	4
	Non-smoker	2
Haematuria	Gross	6
	Microscopic	2
Maximum score		14

*Total score of 10 or more indicates high risk for bladder cancer

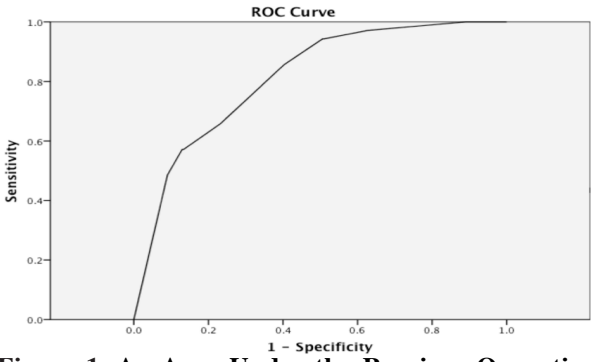

Figure 1. An Area Under the Receiver Operating Characteristic Curve of 80.4% Demonstrates that the Scoring System has Good Accuracy

A scoring system to predict the probability of having bladder cancer among patients with haematuria was proposed. The scoring system had 4 clinical parameters, namely age, gender, history of smoking and whether the haematuria was gross or microscopic in nature. The total score ranged from 6 to 14 (Table 1). It was found to have good accuracy with an area under the ROC curve of 80.4% (Figure 1). A score of 10 or more places the patient at a higher risk of harbouring bladder cancer. By using the cut-off value of 10, this scoring system had a sensitivity of 90.0% and a specificity of 55.7%. The PPV and NPV were 35.8% and 95.3% respectively.

Discussion

Patients with haematuria are usually referred to the urologist for further assessment and management. They could either present with gross haematuria that is visible to the naked eye, or microscopic haematuria that is detected by urinalysis or urinary microscopy. While most cases of haematuria have benign aetiologies, a fair proportion is caused by malignancies. In a review article of the management of patients with haematuria, the authors classified heamaturia into "visible" and "non-visible" haematuria. They devised an algorithm of management in which it was recommended that all visible haematuria

and symptomatic non-visible haematuria be evaluated by the urologist. Patients with asymptomatic non-visible haematuria and over the age of 40 years also warranted a urologic evaluation in this algorithm (Kelly et al., 2000). Bladder cancer most commonly presents with haematuria, and indeed bladder cancer is the commonest malignancy detected in patients with either macroscopic or microscopic haematuria (Grossfeld et al., 2001; Edwards et al., 2006; Messing, 2007). In a study of 4020 patients with haematuria, 10.3% had bladder cancer, 1.8% had other upper urinary tract malignancies, 8.4% had urinary stones, and the remaining 79.6% had no disease detected. (Edwards et al., 2006).

In large studies of patients with haematuria, 10.3-11.9% were diagnosed with bladder cancer and they accounted for the majority of all patients with malignancies (Khadra et al., 2000; Edwards et al., 2006). Cha et al reported a higher bladder cancer prevalence of 20.7% in a group of patients with haematuria, which is quite close to the prevalence found in the present study (Cha et al., 2012). Patients with gross haematuria are more likely to have bladder cancer than those with microscopic haematuria. Gross haematuria has a PPV of 22% of detecting bladder cancer whereas 7.1-8.1% of patients with microscopic haematuria have bladder cancer (Buntinx and Wauters 1997; Messing 2007). These figures show that not only should gross haematuria be taken seriously, even microscopic haematuria cannot be treated lightly. They warrant a thorough urologic assessment to exclude malignancies of the urinary system, and in particular bladder cancer.

A complete urologic evaluation for a patient with haematuria includes repeated urinalysis, urine culture, upper urinary tract imaging, cystoscopic examination (CE) and urinary cytology (Grossfeld et al., 2001). CE is the most reliable method to assess the bladder for cancer (Khadra et al., 2000; Grossfeld et al., 2001; Messing, 2007). There are urine-based tumour marker detection techniques such as a point-of-care assay for the NMP22 protein marker and another multitarget fluorescence in situ hybridisation (FISH) assay, which are developed to diagnose bladder cancer in patients with haematuria (Messing, 2007; Lotan et al 2009). However the sensitivity of such methods for the detection of bladder cancer is only in the region of 50% (Grossman et al., 2005; Messing, 2007).

Several nomograms have been developed to quantify the risk of bladder cancer in patients presenting with haematuria (Lotan et al., 2009; Cha et al., 2012). They usually combine clinical risk factors with an investigation such as a urine-based tumour marker or urinary cytology. While they have improved accuracy over either tumour markers or urinary cytology alone, they can underestimate the probability of bladder cancer (Lotan et al., 2009). To date, there is no single test that can replace the list of investigations that a patient with haematuria has to go through. Neither is there a non-invasive method other than CE that can safely exclude the presence of bladder cancer in a patient with haematuria (Khadra et al., 2000; Grossfeld et al., 2001; Messing, 2007; Lotan et al., 2009).

Bladder cancer survival is significantly better when detected at an early stage (Grossman et al., 2005; Messing, 2007; Madeb and Messing, 2008). The 5-year survival rate is in excess of 90% if the tumour is confined to the mucosa. But any delay in the treatment was shown to have a detrimental effect on the survival of T1 bladder cancer (Wallace et al., 2002). Once there is muscle invasion, the 5-year survival rate drops to less than 50% (Grossman et al., 2005). Delays before radical cystectomy for muscle-invasive bladder cancer can further worsen the survival outcome of this group of patients (Gore et al., 2009). This usually compels us to perform the investigations as soon as possible.

The need for early diagnosis and treatment of bladder cancer places a substantial burden on the urology units because of the need for CE. Although CE is considered an office or daycare procedure, it requires specialised equipment and well-trained medical personnel to perform it effectively and efficiently. The cystoscope needs to be cleaned and sterilised before being used for the next patient. Hence, there is a limit to the number of patients who can be assessed at any one session. This potentially results in late diagnosis for some patients who really harbour bladder cancer because they could not be assessed early enough. Therefore, it would be useful to identify the patients with haematuria who are at a higher risk of having bladder cancer. This group of patients can then be assessed earlier and hopefully improve the detection rate of early stage bladder cancer.

The aforementioned nomograms could be used to identify patient who are more at risk of having bladder cancer. However, the need for specialised test kits or urinary cytology limits the feasibility of adopting these nomograms in many urology units. The scoring system that was developed in the present study aims to utilise only clinical parameters to risk stratify these patients into high or low risk groups. It is therefore economical and simple to use. The 4 parameters used were age, gender, history of cigarette smoking, and the presence of gross haematuria. They were each given scores based on the strength of their association with bladder cancer. For instance, the presence of gross haematuria was given the greatest score because it was strongly related to the diagnosis of bladder cancer (OR=15.74, 95%CI:6.57-37.70).

Although the mean age of the bladder cancer and non-cancer group did not differ significantly in this study, the general trend that bladder cancers are found in the more advanced age patients was still evident here. A cut-off age of 50 years was chosen because numerous studies have considered ages above this to be a risk factor for bladder cancer (Messing et al., 1987; Alishahi et al., 2002; Madeb and Messing, 2008). The male gender, history of cigarette smoking and gross haematuria are all known to confer a greater risk of bladder cancer (Summerton et al., 2002; Grossman et al., 2005; Lotan et al., 2009). This was confirmed in univariate analyses of these factors in this study. Gross haematuria seemed to be the risk factor most heavily associated with bladder cancer, followed by history of cigarette smoking and gender. Even though Summerton et al considered positive history of UTI a risk factor in their study, it was not found to be significant in the present study (Summerton et al., 2002). It was therefore

not included in the development of this scoring system.

This scoring system has a good accuracy of 80.4% in detecting bladder cancer among patients with haematuria. A patient with score of 10 or more is at a higher risk of having bladder cancer. This threshold figure gives the scoring system a sensitivity of 90% and specificity of 55.7%. This means that 9 out of 10 patients with haematuria and bladder cancer will be correctly scheduled for early urologic assessment. Importantly, more than half of all patients who present with haematuria and do not have bladder cancer can be given later appointments for assessment. This will allow the resources of the urology unit to be channeled to patients who are more likely to require early attention.

Given a bladder cancer prevalence of 21.5% among this study population, the scoring system had a PPV of 35.8% and NPV of 95.3%. The implication is that more than a third of those stratified into the high-risk group and undergo early urologic evaluation will have bladder cancer. This seems to be an acceptable yield since no extra investigation tools are needed to stratify the patients. Equally useful is that patients who are considered low-risk based on the scoring system, can be informed that there is more than 95% chance that they do not have bladder cancer. This can provide them reassurance and comfort, while waiting for full urologic evaluations to be carried out.

The retrospective nature of this study limits the completeness of the data obtained for analysis. Every effort was made to ensure that only patients with complete and accurate data were included in the final analysis. This study also has the inherent problem of retrospective studies in which selection bias occurs. Nevertheless, we tried to reduce this effect by including the majority of the patients in our database through diligent search of critical information in every patient's medical records. Although the current performance of this scoring system seems impressive, we recognise the need for prospective validation. The validity of this scoring system is being evaluated with prospectively collected data, currently ongoing in our institution.

It should be emphasized that this scoring system, or any other currently available nomogram cannot replace the standard urologic evaluation of patients with haematuria. The scoring system created in the present study is only intended to assist urologists and medical practitioners in deciding the urgency of assessment that the patients need. The quest for a non-invasive and reliable method in diagnosing bladder cancer continues. Until then, CE remains the best tool we have for this purpose. Nevertheless, we can improve the survival outcome of bladder cancer by early detection and treatment. It is to this end that scoring systems and nomograms can play a role by identifying those at a greater risk for timely urologic evaluation.

In conclusion, haematuria is a common presentation of bladder cancer that demands serious attention. Early detection of bladder cancer is known to confer survival benefits. A scoring system that has the potential to stratify patients with haematuria into high or low risk for bladder cancer has been developed. Stratification of patients in this way can help identify the high-risk patients for early urologic evaluation.

References

Alishahi S, Byrne D, Goodman CM, et al (2002). Haematuria investigation based on a standard protocol: emphasis on the diagnosis of urological malignancy. *J R Coll Surg Edinb*, **47**, 422-7.

Buntinx F, Wauters H (1997). The diagnostic value of macroscopic haematuria in diagnosing urological cancers: a meta- analysis. *Fam Pract*, **14**, 63-8.

Cha EK, Tirsar LA, Schwentner C, et al (2012). Accurate risk assessment of patients with asymptomatic hematuria for the presence of bladder cancer. *World J Urol*, **30**, 847-52.

Edwards TJ, Dickinson AJ, Natale S, et al (2006). A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. *BJU Int*, **97**, 301-5.

Gore JL, Lai J, Setodji CM, et al (2009). Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. *Cancer*, **115**, 988-96.

Grossfeld GD, Litwin MS, Wolf JS Jr, et al (2001). Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy--part II: patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. *Urology*, **57**, 604-10.

Grossfeld GD, Litwin MS, Wolf JS, et al (2001). Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy--part I: definition, detection, prevalence, and etiology. *Urology*, **57**, 599-603.

Grossman HB, Messing E, Soloway M, et al (2005). Detection of bladder cancer using a point-of-care proteomic assay. *JAMA*, **293**, 810-6.

Kelly JD, Fawcett DP, Goldberg LC (2009). Assessment and management of non-visible haematuria in primary care. *BMJ*, **338**, 227-32.

Khadra MH, Pickard RS, Charlton M, et al (2000). A prospective analysis of 1930 patients with hematuria to evaluate current diagnostic practice. *J Urol*, **163**, 524-7.

Lotan Y, Capitanio U, Shariat SF, et al (2009). Impact of clinical factors, including a point-of-care nuclear matrix protein-22 assay and cytology, on bladder cancer detection. *BJU Int*, **103**, 1368-74.

Madeb R, Messing EM (2008). Long-term outcome of home dipstick testing for hematuria. *World J Urol*, **26**, 19-24.

Messing E (2007). Markers of detection. *Urol Oncol*, **25**, 344-7.

Messing EM, Young TB, Hunt VB, et al (1987). The signiWcance of asymptomatic microhematuria in men 50 or more years old: findings of a home screening study using urinary dipsticks. *J Urol*, **137**, 919-22.

Summerton N, Mann S, Rigby AS, et al (2002). Patients with new onset haematuria: assessing the discriminant value of clinical information in relation to urological malignancies. *Br J Gen Pract*, **52**, 284-9.

Wallace DMA, Bryan RT, Dunn JA, et al (2002). Delay and survival in bladder cancer. *BJU Int*, **89**, 868-78.