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Estimated prediction of urinary tract neoplasms using the identify risk calculator in patients with haematuria

Beatriz Gutiérrez Hidalgo, Juan Gómez Rivas, Irene de la Parra, Rommel Arévalo, M. Isabel Galante Romo, Marco Ciappara, Enrique Redondo, Jesús Moreno-Sierra

Department of Urology, Hospital Clínico San Carlos, Complutense University, Madrid, Spain
Health Research Institute, Hospital Clínico San Carlos, Madrid, Spain

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Corresponding author
Beatriz Gutiérrez Hidalgo
Department of Urology, Hospital Clínico San Carlos, Complutense University, Avenida de Filipinas 36, escalera A, 2° Derecha, Madrid, Spain
bea_gutih@hotmail.com

Introduction The classification of patients studied for haematuria into risk groups is important for early diagnosis of urinary tract cancers and optimising healthcare resources. This study aims to evaluate the role of the IDENTIFY calculator in the initial study of these patients and its use for classifying patients into risk groups.

Material and methods A study of patients with haematuria was performed from June 2020 to June 2022. They were classified into risk groups using the IDENTIFY calculator. Final diagnosis of bladder neoplasia between the risk groups was compared. Receiver operating characteristic (ROC) curves were calculated according to the percentage of risk obtained with the calculator and the final diagnosis of bladder neoplasia.

Results We included 255 patients. Imaging tests were positive for bladder cancer in 39 patients (15.3%). Transurethral resection of bladder tumour was performed in 39 cases; 4 were negative, 18 cases Ta, 2 cases T1, 14 cases T2, and one case carcinoma *in situ* (CIS). The final diagnosis was bladder neoplasia in 35 patients (13.8%). These patients were classified as: one low risk (2.9%), 4 intermediate risk (11.4%), and 30 high risk (85.7%); p <0.001. ROC curves were calculated, with an AUC (area under curve) of 0.89; p <0.001.

Conclusions Patients classified into the high-risk group were more frequently diagnosed with bladder cancer than other risk groups. The IDENTIFY risk calculator is a simple and easy-to-use tool with acceptable discrimination in the diagnosis of urinary tract tumours, specifically bladder cancer.

Key Words: haematuria ‹› bladder cancer ‹› risk calculator ‹› diagnosis

INTRODUCTION

Urinary tract tumours are common in our environment, with bladder tumours being the most prevalent. They are associated with a moderate risk of morbidity and mortality, generating an impact on healthcare system resources [1]. Bladder cancer is the fourth most frequent tumour in men worldwide, being the seventh most frequent tumour when considering both genders [2].

Approximately 75% of bladder cancers are non-muscle invasive (NMIBC), affecting the mucosa (Ta, carcinoma *in situ* [CIS]) or submucosa (T1); the determination of infiltration in the muscular layer (invasive, T2) is essential when deciding on the therapeutic approach [3].

There are multiple associated risk factors, the most important of which is smoking (present in up to 50% of cases). Other related factors are occupational exposure, history of radiotherapy, and family history, among others [4].

The most frequent clinical presentation in this type of tumour is haematuria, which can be microscopic or macroscopic. However, other benign causes can justify it, so it is important to determine which type of patients have a higher risk

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of presenting bladder cancer to carry out a directed study. Given that some diagnostic methods in the study of haematuria are invasive, it is important to correctly guide the differential diagnosis [5].

In 2021, the IDENTIFY group presented a study with the largest cohort of patients with suspected urinary tract neoplasia, the primary objective of which was to study the prevalence of these tumours [6]. Based on these results, they developed a multivariable predictive model: the IDENTIFY Calculator (https://bursturology.com/identify-calculator/). Developed by the British Urology Researchers in the Surgical Training (BURST) group, it allows patients to be classified according to the estimated risk of urinary tract neoplasia based on the items described below [7].

The objective of this study is to assess the risk of presenting urinary tract tumours, especially bladder cancer, in patients evaluated for haematuria in our centre using the IDENTIFY calculator.

As a secondary objective, we performed a descriptive analysis of patients studied for haematuria.

MATERIAL AND METHODS

This retrospective study included patients (n = 255) assessed for haematuria in our centre from June 2020 to June 2022. Inclusion criteria were patients ≥16 years old assessed for macrohaematuria or microhaematuria, with a minimum follow-up time of 6 months. Exclusion criteria were the previous diagnosis of urinary tract cancer or failure to fulfil the previously described inclusion criteria.

Sociodemographic aspects, type of haematuria (microscopic and macroscopic), accompanying symptoms, diagnostic tests, performance of transurethral resection of bladder tumours (TURBT), and anatomopathological results were collected. We considered positive for bladder tumour the cases confirmed by pathological anatomy after TURBT.

During the first evaluation, most of the patients were studied by ultrasound and cytology. In the case of negative or doubtful ultrasound, cystoscopy was indicated. In patients with larger lesions, a complementary computed tomography (CT) urogram was performed.

Using the IDENTIFY calculator, we divide patients according to the risk of presenting urinary tract neoplasia. Based on these items, the calculator gives a percentage estimated risk of urinary tract neoplasia, dividing patients into very low-risk (<1%), low-risk (1–5%), intermediate-risk (5–20%), and high-risk >20%.

Statistical analysis

We made a comparison according to the type of haematuria and the frequency of diagnosis of bladder cancer, the need for TUR, and anatomopathological findings, as well as a comparison of the final diagnosis of bladder cancer with the risk groups obtained with the IDENTIFY calculator, using the χ^2 test statistical study.

The assessment of the association between the percentage risk of the calculator and the diagnosis of bladder neoplasia was performed using the Mann-Whitney test. We calculated ROC (receiver operating characteristic) curves according to the percentage of risk obtained with the calculator and the final diagnosis of bladder neoplasia, using the Youden index. P-value <0.05 was selected as a statistically significant value. The statistical program used was IBM SPSS version 26 software.

Bioethical standards

The study was approved by Clínico San Carlos Hospital (Madrid, Spain) internal Ethics Comittee, under code 22/516-E.

RESULTS

Overall descriptive

A total of 255 patients were studied for haematuria in our centre from June 2020 to June 2022. The items evaluated by the calculator with the demographic and clinical information of the patients are described in Table 1.

The risk calculator stratified patients into very low risk (12 patients, 4.7%), low risk (68 patients, 26.6%), intermediate risk (106 patients, 41.6%), and high risk (69 patients, 27.1%).

Regarding imaging tests, 252 urinary tract ultrasound scans were performed, being diagnostic of bladder cancer in 28 cases (11% of ultrasounds performed) and negative in 140 patients (54.9%). In cases of negative ultrasound or not clearly suggestive of a bladder tumour, a cystoscopy was indicated. Cystoscopy was performed directly in only 3 cases (1.18%), and all had an adjuvant CT urogram. A total of 167 cystoscopies were performed (65.5%), of which 25 revealed a bladder tumour (15% of the total of cystoscopies). Urine cytology was performed in 244 patients (95.7% of cases). The results obtained were as follows: 220 negative (90.2%), 12 atypical (4.9%), 4 suspicious for malignancy (1.6%), and 8 positive for high-grade urothelial neoplasia (3.3%). Of the total patients,

123 (48.2%) were additionally studied with CT urogram, showing bladder neoplasia in 16 cases (13.1%). In 2 cases there was concomitant evidence of upper urinary tract neoplasia (UUT). The rest of the CT results were 57.4% negative (70 cases) and 29.5% benign pathologies (36 cases). In the very low- and low-risk groups no bladder tumour was seen in ultrasound, and only in 2 cases was bladder tumour observed in cystoscopy and one in CT urogram in the low-risk group.

Diagnostic tests showed bladder tumours in 39 patients (15.29%), although 35 patients (13.8%) were finally diagnosed with bladder cancer confirmed by pathological anatomy. Two patients had upper urinary tract neoplasia concurrent with bladder neoplasia (0.8%). Other diagnoses were as follows: 2 (0.8%) prostate neoplasia, 109 (42.7%) benign diseases, and in 109 cases (42.7%) the study was negative.

Of the anticoagulated patients (29 cases, 11.4%), bladder tumour was confirmed in 6 cases (20.68% of patients with anticoagulant therapy).

TURBT was performed in 39 patients (15.3%). The anatomopathological results were as follows: 18 Ta (51.4%), 1 CIS (2.9%), 2 T1 (5.7%), and 14 T2 (40%). Four cases were negative for malignancy. The anatomopathological results in the anticoagulated patients were 5 cTa (83.33%) and 1 cT2 (16.67%).

Cystectomy was performed in 8 patients. The anatomopathological findings of the surgical specimens were: 3 ypT0 (37.5%), 1 pT2 (12.5%), 2 pT3 (25%), and 2 pT4 (25%). The anatomopathological results of the lymphadenectomy were 6 pN0 (75% of the lymphadenectomies), 1 pN1 (12.5%), and 1 pN2 (12.5%). In 2 patients, a nephroureterectomy was performed within the same surgical procedure (one case pT1 and one case pT3).

Table 1. *IDENTIFY calculator data of our study population*

Calculator item	Frequency (n)	Percentage (%)
Type of haematuria		
Microhaematuria	134	52.5
Macrohaematuria	121	47.5
Gender		
Female	100	39.2
Male	155	60.8
Smoking history		
Non-smokers	107	42
Former smokers	92	36.1
Active smokers	56	22
Family history of urothelial cancer (yes)	2	0.8
Previous investigation of benign haematuria (yes)	33	12.9
Urinary tract infection (UTI)		
No	227	89.0
Single UTI	17	6.7
Recurrent UTI	11	4.3
Catheter use (yes)	8	3,1
Previous pelvic radiation therapy (yes)	2	0.8
Suprapubic pain or dysuria (yes)	59	23.1
Anticoagulated (yes)	29	11.4

Results according to the IDENTIFY risk calculator

Of patients with an anatomopathological diagnosis of Ta, 16 were high risk (45.71%) and 2 intermediate risk (5.72%); the 2 cases of T1 (5.72%) were both classified as high risk; of the T2, 2 were intermediate risk (5.72%) and 12 high risk (34.29%). The only case with CIS (2.8%) was classified as low risk. When considering the histological grade, of the cases classified as high grade (16 cases), 12 were patients classified as high risk, 3 as intermediate risk, and one as low risk. Finally, of the patients who underwent radical cystectomy, all were classified as high risk (7 cases; 87.5%), except for one case classified as intermediate risk (12.5%). The diagnosis of bladder cancer according to risk groups was 30 cases in the high-risk group (85.7% of the patients diagnosed with bladder cancer), 4 cases in the intermediate-risk group (11.4%), and one case in the low-risk group (2.9%), $p < 0.001$. No patient in the very low-risk group was diagnosed with bladder cancer or urinary tract neoplasia (Figure 1).

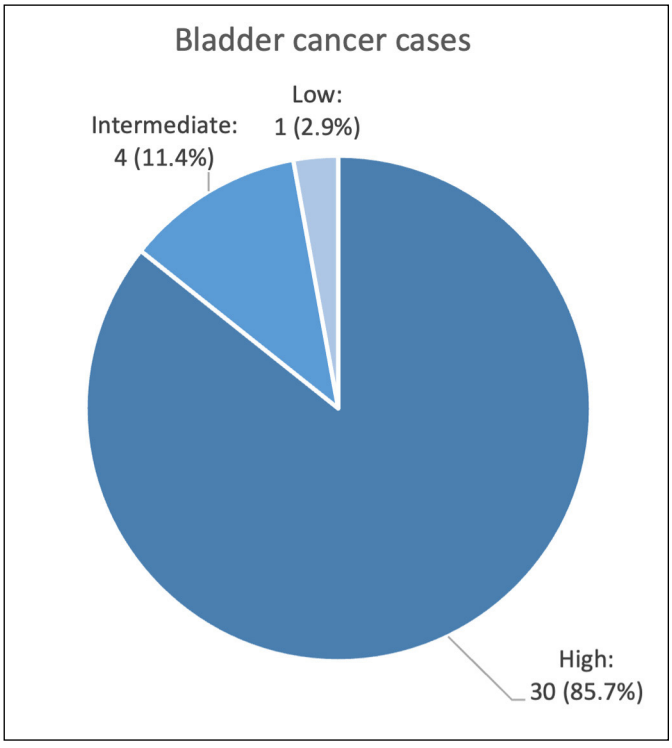

Figure 1. *Diagnosis of bladder cancer according to the distribution of risk groups.*

The association between the percentage (%) of calculator risk and the diagnosis of bladder cancer was assessed, with statistically significant values ($p < 0.001$). Finally, based on the percentage (%) of risk calculated by the IDENTIFY calculator and the number of cases diagnosed with bladder neoplasia, the ROC curves were calculated, with an AUC (area under curve) of 0, 89 with a confidence interval of 95%, $p < 0.001$. The calculated cut-off point with the highest sensitivity and specificity (0.943 and 0.755, respectively) is 16.70% (Figure 2).

Micro/macrohaematuria comparison

Of the total of bladder diagnoses, 33 cases (94.28%) debuted with macroscopic haematuria, while 2 cases (5.72%) were diagnosed after microscopic haematuria study. We did not identify statistically significant differences between smoking and type of haematuria ($p = 0.632$). The final diagnosis of bladder tumour was more frequent in the group of patients with macrohaematuria (33 cases [27.3% of patients with gross haematuria] vs 2 cases [1.5% patients with microhaematuria]; $p < 0.001$), as well as the need to undergo TURBT (36 vs 3; $p < 0.001$). Of the patients who finally underwent radical cystectomy, all had presented macroscopic haematuria ($p < 0.001$).

DISCUSSION

In the descriptive analysis, the most frequently diagnosed urinary tract tumour was bladder cancer. This was more frequent in males and in patients with smoking history. In addition, bladder cancer was more frequent in patients with macrohaematuria. These results are consistent with data from the literature [6–9]. The mean age of our cohort was 64 years, similar to the recent publication on urinary neoplasm prevalence in a Spanish cohort based on data from the IDENTIFY study, whose mean age was 67 years [10].

Multiple causes of haematuria can be benign or malignant, although one of the most important, bladder neoplasia, must be ruled out [11, 12]. Given that some tests used in the diagnosis of urinary tract neoplasia are invasive [13], such as cystoscopy that is not free of complications (urinary tract infections, bleeding, or episodes of acute urinary retention, among others), it is important to use tools that allow us to select which patients require a complete study with greater urgency and in which patients invasive tests could be delayed or even avoided [5].

For the initial study of haematuria, tests such as urological ultrasound and cystoscopy are contemplated, in addition to urine cytology [14–16].

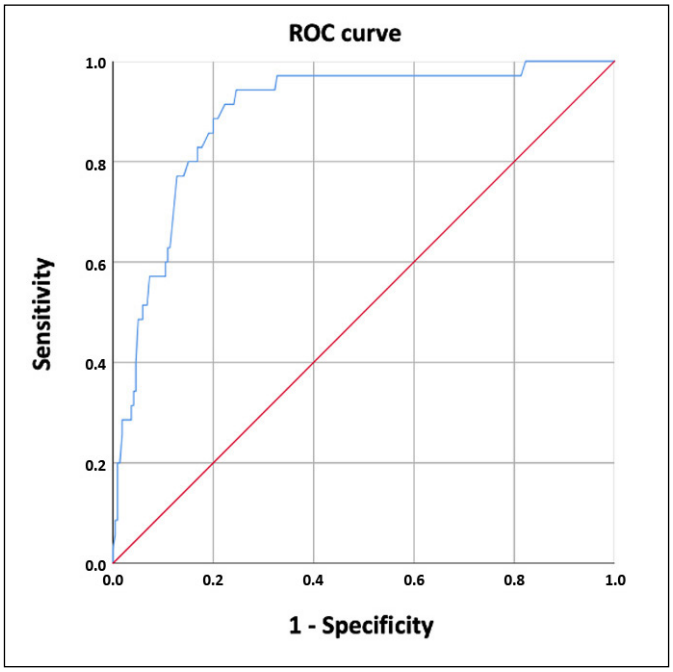

Figure 2. *Distribution of ROC curve.*

For the evaluation of the upper urinary tract, the best diagnostic test is CT urogram [17, 18]. The most frequent test performed in our study was ultrasound, with 11% of findings of bladder tumour. In 15 cases TURBT was performed directly without cystoscopy. The second test most frequently performed was cystoscopy, with 15% of findings of bladder tumour. Urine cytology was collected in 90% of patients, being positive in 3.3% of cases and suspicious in 1.6%. CT urogram was performed in almost half of the cases, with a finding of bladder tumour in 13.1% and in 2 cases concomitant upper urinary tract neoplasia. It must be said that in all cases of CT there was a previous diagnosis of bladder tumour in ultrasound or cystoscopy. Ultrasound was negative in very low- and low-risk patients, and cystoscopy was negative in the very low-risk group, with discovery of bladder tumour in 2 low-risk cases. Many markers are being studied for the diagnosis of bladder cancer, thus avoiding cystoscopy [19, 20]. So far, none has been validated in daily clinical practice, although there are promising results in several of them, such as Epicheck, Cx-Bladder, ADX-Bladder, and Xpert Bladder, among others [3]. In 2022, Duggan et al. developed gender-differentiated algorithms, using urinary and blood markers associated with clinical factors, to improve initial care in patients with haematuria [5].

Anticoagulant therapy is an important aspect to consider when evaluating patients with haematuria. Jakus et al. [21] observed that anticoagulated

patients had more favourable histopathological grades and stage. In our cohort, 20% (6 cases) of anticoagulated patients were diagnosed of bladder tumour. All cases were cTa, apart from one case that was cT2. This would align with their results, but we have a small sample size.

The IDENTIFY risk calculator is offered as an initial support tool for decision-making when assessing patients with haematuria based on clinical history data without the need for blood or urine markers. It is proposed as a simple, easy-to-use application that allows us to guide and stratify the patients according to their risk of presenting urinary tract cancers. It is a free mobile, tablet, or computer application called the "IDENTIFY risk calculator". It can be oriented to urologists or primary care consultations, always in the hands of physicians familiar with urological pathologies.

When comparing patients in our study according to the tumour risk calculated, we found that the diagnosis of bladder cancer was more frequent in the high-risk group. Of the total patients diagnosed with bladder cancer, more than 80% were classified as high-risk patients. In contrast, none of the patients in the very low-risk group were diagnosed with a bladder neoplasm, and only one patient of the 68 patients in the low-risk group had a bladder tumour. With these data we could consider avoiding an initial, more invasive study in patients classified in the low- or very low-risk group, giving higher priority to patients in the high-risk and intermediate-risk groups. It should be noted that the need for radical cystectomy was also greater in patients included in the high-risk group.

In our series of patients, up to 42% presented a negative result of the diagnostic tests performed. A more directed study of the patient from the beginning of the consultation may help to avoid unnecessary cystoscopies or to avoid excess ionising radiation by avoiding the performance of a CT urogram. Given that more than 90% of the patients diagnosed with bladder cancer presented macroscopic haematuria as the reason for consultation and only 2 cases presented microscopic haematuria, we could consider the use of this tool, especially in patients who consult for microhaematuria. One of the limitations of this calculator is that it does not consider the degree of intensity of smoking or the intensity of microhaematuria. Furthermore, it could overestimate the risk of haematuria in patients with several risk factors. Although the diagnosis of bladder cancer was more frequent in high-risk patients, 3 of them had a negative diagnosis after TURBT. Of the patients who underwent TURBT with a negative anatomopathological result, 3 cases were included in the high-risk group and one case in the low-risk group. The diagnosis in the 4 cases was made by cystoscopy. The role of this tool in the initial diagnosis of bladder cancer and the impact of its use in healthcare practice is yet to be determined. Recently, Khadhouri et al. [22] published the results of the external validation of this calculator in a cohort of 3,582 patients of multicentre origin (in which we participated along with other centres), showing an AUC of 0.78, with adequate accuracy and discrimination to predict the presence of urinary tract cancer. We calculated the ROC curve in our cohort of patients, with an excellent discriminative capacity for finding bladder cancer, although it is not a large sample size. The cut-off point with the highest sensitivity and specificity was 16%. This percentage is within the intermediate-risk group. Above this value, we could consider directing diagnostic studies more precisely and earlier because of the suspected tumour as the cause of haematuria. More studies are needed to establish these observations with greater certainty.

Regarding the limitations of this study, the retrospective data collection and the small sample size of a single centre make the interpretation and extrapolation of these data difficult. Further studies on this tool will be necessary. However, the recent data from the BURST group performing external validation of this calculator are promising regarding its usefulness.

CONCLUSIONS

A targeted haematuria study based on individual patient risk can help direct studies more precisely and in a more individualised manner, avoiding unnecessary invasive tests in some cases. The IDENTIFY calculator is shown to be a simple and easy-to-use tool that can help in initial decision-making during patient management.

Based on our data and a multicentre study with a larger sample size, we can say that it shows acceptable discrimination in the diagnosis of urinary tract tumours, specifically bladder cancer. Further studies will be necessary to see its impact on daily healthcare practice.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

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ETHICS APPROVAL STATEMENT

The study was approved by Clínico San Carlos Hospital (Madrid, Spain) internal Ethics Comittee, under code 22/516-E.

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