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Urothelial Cancer

Developing a Diagnostic Multivariable Prediction Model for Urinary Tract Cancer in Patients Referred with Haematuria: Results from the IDENTIFY Collaborative Study

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Abstract

Background: Patient factors associated with urinary tract cancer can be used to risk stratify patients referred with haematuria, prioritising those with a higher risk of cancer for prompt investigation.

Objective: To develop a prediction model for urinary tract cancer in patients referred with haematuria.

Design, setting, and participants: A prospective observational study was conducted in 10 282 patients from 110 hospitals across 26 countries, aged ≥16 yr and referred to secondary care with haematuria. Patients with a known or previous urological malignancy were excluded.

Outcome measurements and statistical analysis: The primary outcomes were the presence or absence of urinary tract cancer (bladder cancer, upper tract urothelial cancer [UTUC], and renal cancer). Mixed-effect multivariable logistic regression was performed with site and country as random effects and clinically important patient-level candidate predictors, chosen *a priori*, as fixed effects. Predictors were selected primarily using clinical reasoning, in addition to backward stepwise selection. Calibration and discrimination were calculated, and bootstrap validation was performed to calculate optimism.

Results and limitations: The unadjusted prevalence was 17.2% (n = 1763) for bladder cancer, 1.20% (n = 123) for UTUC, and 1.00% (n = 103) for renal cancer. The final model included predictors of increased risk (visible haematuria, age, smoking history, male sex, and family history) and reduced risk (previous haematuria investigations, urinary tract infection, dysuria/suprapubic pain, anticoagulation, catheter use, and previous pelvic radiotherapy). The area under the receiver operating characteristic curve of the final model was 0.86 (95% confidence interval 0.85–0.87). The model is limited to patients without previous urological malignancy.

Conclusions: This cancer prediction model is the first to consider established and novel urinary tract cancer diagnostic markers. It can be used in secondary care for risk stratifying patients and aid the clinician's decision-making process in prioritising patients for investigation.

Patient summary: We have developed a tool that uses a person's characteristics to determine the risk of cancer if that person develops blood in the urine (haematuria). This can be used to help prioritise patients for further investigation.

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1. Introduction

Haematuria is the most common presentation of suspected urinary tract cancers and is the leading cause of referral to secondary care amongst the urological cancer pathways [1,2]. Bladder cancer is the most prevalent cancer diagnosis in these patients, whilst upper tract urothelial cancers (UTUCs) and renal cell carcinomas (RCCs) are rarer [3,4]. Urinary tract cancers carry high morbidity and mortality [5,6], and early diagnosis is important. The investigation of haematuria poses a huge global health burden as there are many causes, including benign pathology [7]. Reducing unnecessary investigations whilst identifying clinically important urinary tract cancers is an important unmet need [8]. As a result, risk markers should be used to select patients for referral and to determine urgency for further investigation. A recent prediction model to identify bladder cancer in patients with haematuria was developed to recommend a threshold for investigation [9]. Four well-established risk markers were used to predict bladder cancer (type of haematuria, age, sex, and smoking history) [7,10–13]. However, the model neither predicted upper tract cancer nor included other important clinical risk markers such as anticoagulation, previous radiotherapy, and urinary tract infections, which have been described in the literature [14–16].

The IDENTIFY study is the largest prospective cohort study of patients referred with suspected urinary tract cancer. One aim of the study was to develop a model to predict urinary tract cancer in patients referred with haematuria, using several predetermined clinical risk markers. The effects of such a wide range of potential risk markers have not been investigated simultaneously in a study of this scale. This is necessary to account for the complex interplay of factors related to an individual's particular risk of cancer. Individualised risk predictions can then guide a shared decision-making process between the patient and the clinician about further investigation.

2. Patients and methods

2.1. Study design and source of data

The IDENTIFY study was an international prospective cohort study in patients referred to secondary care with suspected urinary tract cancer [17]. Further details of the study including the adjusted prevalence of cancer have been published [4]. Data collected included the reason for referral, baseline demographic information, clinical history, urine analysis, cytology, imaging findings, cystoscopy findings, histopathology from biopsies or surgery, and multidisciplinary team decisions.

In this analysis, we used the cohort of patients with haematuria (visible or nonvisible haematuria) to develop the prediction model. Nonvisible haematuria was defined as a trace or more on urinalysis, or three or more red blood cells per high power field on microscopy. Microscopy was not required to confirm a urinalysis positive for blood. Patient data were obtained from hospital records of consecutive patients attending a secondary care "haematuria clinic" for a flexible cystoscopy between December 2017 and December 2018. Patients were followed up until their haematuria investigations were concluded and a diagnosis was confirmed or ruled out, as per the judgement of the clinical care team. We report this study according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement (Supplementary material) [18].

2.2. Participants

We included patients aged ≥16 yr, with haematuria, who were referred to a urologist and underwent investigation for suspected urinary tract cancer. The investigations performed were determined by the urologist's standard practice. Patients were excluded if they had a previous or known diagnosis of primary urological cancer or were undergoing investigations for the recurrence of a primary urological cancer.

2.3. Outcome

The primary outcome was the absence or presence of any urinary tract cancer (defined as bladder cancer, UTUC, or RCC) [4,17]. We defined cancer as per Supplementary Table 1 [19,20]. We developed the main model to predict urinary tract cancer. This was derived from three secondary prediction models, one for each type of urinary tract cancer. The secondary outcomes were the absence or presence of each type of urinary tract cancer in their respective models.

2.4. Candidate predictors

Candidate predictors for each type of cancer were chosen based on clinical reasoning and evidence from literature. Table 1 shows the candidate predictors that were used to develop the initial models for each type of cancer. These were chosen *a priori* as clinically relevant predictors of urinary tract cancer, by the research steering committee and clinical experts during study design [17].

2.5. Sample size

We used the fixed sample size of 10 282 patients based on the primary goal of the study, which was the estimated prevalence of urinary tract cancers [4,17].

2.6. Statistical analysis methods

We used a multilevel mixed-effect logistic regression model with country and site as random effects, and all other candidate predictors as fixed effects. Age was included as a continuous predictor; all other predictors were categorical. We performed a complete case analysis and did not impute the small proportion of missing data (see the Supplementary material).

We developed separate models for each type of cancer (ie, bladder cancer, UTUC, and RCC) first, as different predictors may be relevant for one type of cancer but not the other. An example is flank pain, which would be hypothesised to be more relevant in UTUC and renal cancer than in bladder cancer. These secondary predictive models for each type of cancer were developed using a combination of clinical judgement and the backward stepwise elimination process for the poorly understood predictors. We initially fitted the full multivariable model and then performed backward stepwise elimination as we were exploring new candidate predictors. Crucially though, we judged the clinical importance of keeping each predictor before it was eliminated, as clinical selection of predictors is more important than statistical methods alone. The performance of each model was reported.

We fitted statistically significant two-way interaction terms that we deemed clinically important and made clinical sense. The rationale for fitting interaction terms was to account for differences in the predictor's effect between subgroups. A p value of <0.05 was considered statistically significant.

Table 1 – List of predictors for bladder cancer, upper tract urothelial cancer (UTUC), and renal cancer

Predictors for all cancers		
Type of haematuria (visible or nonvisible haematuria)		
Age in years		
Sex (male, female)		
Smoking history (current, ex-smoker, never smoker, or unknown)		
High-risk occupation (yes/no or unknown), defined as exposure to occupational hazards associated with bladder cancer, for example, dyes, rubber, textiles, and pesticides		
High-risk travel (yes/no or unknown)—risk of schistosomiasis in freshwater lakes in Africa, South America, or Middle East		
High-risk medications, for example, cyclophosphamide and pioglitazone (yes/no or unknown)		
Episode of urinary tract infection associated with the patient's presentation (none/single/recurrent)		
Anticoagulation (yes/no)—includes warfarin, novel anticoagulant (eg, rivaroxaban, apixaban), antiplatelet (eg, aspirin, clopidogrel), and heparin (any)		
Previous negative investigation for haematuria (yes/no)		
Predictors specific to type of cancer		
Bladder cancer	**UTUC**	**Renal cancer**
Family history of urothelial cancer (yes/no)	Family history of urothelial cancer	Family history of renal cancer
Dysuria or suprapubic pain (yes/no)	Flank pain (yes/no)	Flank pain (yes/no)
Any lower urinary tract symptoms (obstructive/voiding, storage/irritative or mixed)		
The current use of a catheter (yes/no), including urethral, suprapubic, and intermittent		
Ethnicity (White, Asian, Black/African American, other)		
History of previous pelvic radiotherapy (yes/no)		

The predictors used in the predictive model for all urinary tract cancers were selected from all three secondary models, based on the clinical judgement of the study's steering committee. Further detailed statistical analysis methods are included in the Supplementary material.

2.7. Evaluation of performance

The calibration slope, area under the receiver operating characteristic curve (AUC), and decision curve analysis were used to assess the performance of the final predictive model for all urinary tract cancers. The model was internally validated using bootstrap resampling with 200 repetitions, and the optimism was calculated, as per the TRIPOD statement (ie, development of the model in each bootstrap sample) [18]. Furthermore, we evaluated the performance (AUC) of the model in different countries. We chose not to split the data into a development and validation cohort firstly due to the low number of events in the rarer cancers, which would limit the number of candidate predictors in their models, and secondly as we intend to perform a separate study to externally validate the prediction model recommended by the TRIPOD statement.

2.8. Risk calculation tool

The risk score was created using the coefficients from the linear equation of the multivariable logistic regression. We subsequently developed an online calculator rather than a nomogram to predict an individual's probability of urinary tract cancer, for its ease of use and to demonstrate the tool.

2.9. Development of risk score and risk groups

As a guide, we developed risk groups to aid clinicians in determining further investigation. To this end, we defined four categories of cancer risk: very low, low, intermediate, and high. The justification for a very low risk category was to identify a group where investigation may be avoided or delayed. Low-, intermediate-, and high-risk groups are commonly used in clinical practice and reflect a gradient where increasing intensity and urgency of investigation are required. We selected a threshold of <1% predicted risk for the very low group, and 5% and 20% as cut-offs to create low-, intermediate-, and high-risk groups. All thresholds were selected based on clinical reasoning by the study steering committee, as there are no established risk stratification thresholds in use within secondary care in this field. Clinical reasoning was felt to be more appropriate and meaningful than statistical methods for risk thresholds. The observed cancer prevalence from the cohort was cross-checked in each risk group to ensure that they reflected clinically appropriate stratification.

All analyses were performed using Stata version 16.1 (StataCorp, College Station, TX, USA). This study was registered with clinicaltrials.gov NCT03548688, and the study protocol was published in advance [17].

3. Results

3.1. Participants

Figure 1 describes the flow of patients through the study. The prevalence was 17.2% (n = 1763) for bladder cancer, 1.20% (n = 123) for UTUC, and 1.00% (n = 103) for renal cancer. The clinical characteristics of the cohort are described in Table 2 and include patient demographics and all candidate predictors.

3.2. Model development and specification

Supplementary Tables 2–7 show model development for each type of cancer (candidate predictors and number of patients included in each backward stepwise elimination), in addition to the coefficients and odds ratios of variables in their respective final prediction models. The final predictors in the UTUC model were type of haematuria, age, flank pain, and smoking history, and those in the RCC model were type of haematuria and flank pain. There were 11 final predictors in the bladder cancer model. Table 3 shows the main predictive model for urinary tract cancers using selected predictors from all three secondary models. The number of events (cancers) in the main model was 1863 (19.7%).

The AUC of the final model was 0.86 (95% confidence interval [CI] 0.85–0.87), its calibration slope was 1.03 (95% CI 0.98–1.09), and its intercept was –0.01 (95% CI –0.02 to 0.01) [21]. The decision curve analysis shows a net benefit over investigating all or none (Supplementary Fig. 1). The optimism between the bootstrap model and the test model was 0.005 (difference between an apparent model AUC of 0.858 and a corrected model AUC of 0.853). Evaluation of

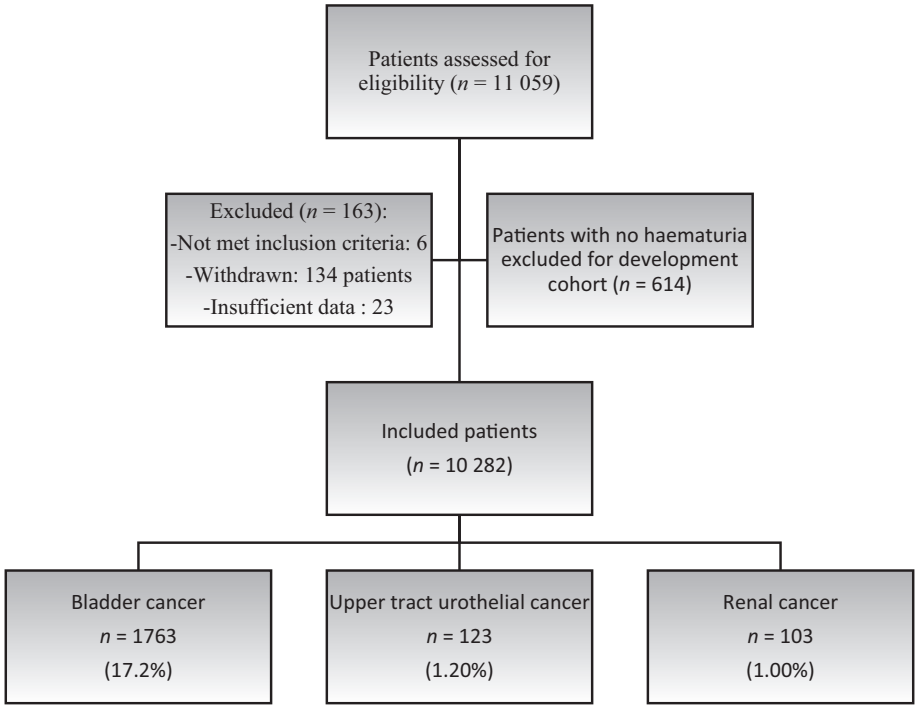

Fig. 1 – Cohort flow diagram.

Table 2 – Patient demographics and clinical characteristics

	Total n (%)	No cancer n (%)	Any urinary tract cancer n (%)	Bladder cancer n (%)	Upper tract urothelial cancer n (%)	Renal cancer n (%)
Total	10 282	8329 (81.0)	1953 (19.0)	1763 (17.1)	123 (1.20)	103 (1.00)
Type of haematuria						
Nonvisible haematuria	3152 (30.7)	2967 (35.6)	185 (9.47)	165 (9.36)	9 (7.32)	13 (12.6)
Visible haematuria	7130 (69.3)	5362 (64.4)	1768 (90.5)	1598 (90.6)	114 (92.7)	90 (87.4)
Age (yr), mean (SD)	64.3 (14.6)	62.8 (14.8)	70.4 (11.9)	70.7 (11.8)	71.9 (11.7)	64.8 (13.1)
Sex						
Female	3853 (37.5)	3384 (40.6)	469 (24.0)	413 (23.4)	40 (32.5)	25 (24.3)
Male	6423 (62.5)	4940 (59.3)	1483 (75.9)	1349 (76.5)	83 (67.5)	78 (75.7)
Other	6 (0.06)	5 (0.06)	1 (0.05)	1 (0.06)	0 (0)	0 (0)
Smoking						
Never smoker	4651 (45.2)	4099 (49.2)	552 (28.3)	477 (27.1)	41 (33.3)	44 (42.7)
Ex-smoker	3066 (29.2)	2267 (27.2)	739 (37.8)	680 (38.6)	38 (30.9)	36 (35.0)
Current smoker	1881 (18.3)	1367 (16.4)	514 (26.3)	471 (26.7)	35 (28.5)	17 (16.5)
Unknown	744 (7.24)	596 (7.16)	148 (7.58)	135 (7.66)	9 (7.32)	6 (5.83)
Occupational risk[a]						
No	8548 (83.1)	6958 (83.5)	1590 (81.4)	1428 (81.0)	102 (82.9)	90 (87.4)
Yes	393 (3.82)	279 (3.35)	114 (5.84)	109 (6.18)	5 (4.07)	2 (1.94)
Unknown	993 (9.66)	784 (9.41)	209 (10.7)	190 (10.8)	13 (10.6)	9 (8.74)
Missing	348 (3.38)	308 (3.70)	40 (2.05)	36 (2.04)	3 (2.44)	2 (1.94)
Medication risk[b]						
No	9203 (89.5)	7459 (89.6)	1744 (89.3)	1575 (89.3)	108 (87.8)	93 (90.3)
Yes	77 (0.75)	57 (0.68)	20 (1.02)	17 (0.96)	2 (1.63)	1 (0.97)
Unknown	628 (6.11)	478 (5.74)	150 (7.68)	137 (7.77)	9 (7.32)	7 (6.80)
Missing	374 (3.64)	335 (4.02)	39 (2.00)	34 (1.93)	4 (3.25)	2 (1.94)
Travel/environmental risk[c]						
No	8761 (85.2)	7030 (84.4)	1731 (88.6)	1566 (88.8)	105 (85.4)	91 (88.4)
Yes	108 (1.05)	99 (1.19)	9 (0.46)	9 (0.51)	0 (0)	0 (0)
Unknown	948 (9.22)	786 (9.44)	162 (8.29)	143 (8.11)	13 (10.6)	10 (9.71)
Missing	465 (4.52)	414 (4.97)	51 (2.61)	45 (2.55)	5 (4.07)	2 (1.94)
UTI history						
None	7873 (76.6)	6155 (73.9)	1718 (88.0)	1548 (87.8)	110 (89.4)	92 (89.3)
Single	1250 (12.2)	1123 (13.5)	127 (6.50)	115 (6.52)	8 (6.50)	6 (5.83)
Recurrent	1018 (9.90)	930 (11.2)	88 (4.51)	80 (4.54)	5 (4.07)	5 (4.85)
Missing	141 (1.37)	121 (1.45)	20 (1.02)	20 (1.13)	0 (0)	0 (0)
Dysuria/suprapubic pain						
No	7909 (76.9)	6300 (75.6)	1609 (82.4)	1442 (81.8)	111 (90.2)	84 (81.6)

(*continued on next page*)

Table 2 (*continued*)

	Total *n* (%)	No cancer *n* (%)	Any urinary tract cancer *n* (%)	Bladder cancer *n* (%)	Upper tract urothelial cancer *n* (%)	Renal cancer *n* (%)
Yes	2144 (20.9)	1830 (22.0)	314 (16.1)	292 (16.6)	11 (8.94)	19 (18.4)
Missing	229 (2.23)	199 (2.39)	30 (1.54)	29 (1.64)	1 (0.81)	0 (0)
Previous haematuria evaluation						
No	9130 (88.8)	7312 (87.8)	1818 (93.1)	1640 (93.0)	115 (93.5)	96 (93.2)
Yes	1023 (9.95)	907 (10.9)	116 (5.94)	104 (5.90)	8 (6.50)	7 (6.80)
Missing	129 (1.25)	110 (1.32)	19 (0.97)	19 (1.08)	0 (0)	0 (0)
Family history of urothelial cancer						
No	9734 (94.7)	7874 (94.5)	1860 (95.2)	1680 (95.3)	119 (96.8)	96 (93.2)
Yes	219 (2.13)	157 (1.88)	62 (3.17)	55 (3.12)	2 (1.63)	5 (4.85)
Missing	329 (3.20)	298 (3.58)	31 (1.59)	28 (1.59)	2 (1.63)	2 (1.94)
LUTS						
None	5991 (58.3)	4765 (57.2)	1226 (62.8)	1096 (62.2)	82 (66.7)	67 (65.1)
Obstructive/voiding	1354 (13.2)	1085 (13.0)	269 (13.8)	247 (14.0)	14 (11.4)	13 (12.6)
Storage/irritative	1800 (17.5)	1543 (18.5)	257 (13.2)	232 (13.2)	15 (12.2)	15 (14.6)
Mixed	1010 (9.82)	826 (9.92)	184 (9.42)	171 (9.70)	12 (9.76)	8 (7.77)
Missing	127 (1.24)	110 (1.32)	17 (0.87)	17 (0.96)	0 (0)	0 (0)
Use of catheter						
No	9833 (95.6)	7930 (95.2)	1903 (97.4)	1715 (97.3)	120 (97.6)	101 (98.1)
Yes	334 (3.25)	301 (3.61)	33 (1.69)	31 (1.76)	3 (2.44)	2 (1.94)
Missing	115 (1.12)	98 (1.18)	17 (0.87)	17 (0.96)	0 (0)	0 (0)
Ethnicity						
White	7930 (77.1)	6288 (75.5)	1642 (84.1)	1482 (84.1)	108 (87.8)	85 (82.5)
Asian	1195 (11.6)	1014 (12.2)	181 (9.27)	170 (9.64)	6 (4.88)	7 (6.80)
Black	297 (2.89)	277 (3.33)	20 (1.02)	14 (0.79)	3 (2.44)	3 (2.91)
Other	518 (5.04)	450 (5.40)	68 (3.48)	60 (3.40)	3 (2.44)	5 (4.85)
Missing	342 (3.33)	300 (3.60)	42 (2.15)	37 (2.10)	3 (2.44)	3 (2.91)
Pelvic radiotherapy						
No	10 043 (97.7)	8125 (97.6)	1918 (98.2)	1731 (98.2)	123 (100)	100 (97.1)
Yes	203 (1.97)	172 (2.07)	31 (1.59)	28 (1.59)	0 (0)	3 (2.91)
Missing	36 (0.35)	32 (0.38)	4 (0.20)	4 (0.23)	0 (0)	0 (0)
Anticoagulation						
No	7306 (71.1)	6027 (72.4)	1279 (65.5)	1153 (65.4)	83 (67.5)	69 (67.0)
Yes	2611 (25.4)	1981 (23.8)	630 (32.3)	569 (32.3)	38 (30.9)	33 (32.0)
Missing	365 (3.55)	321 (3.85)	44 (2.25)	41 (2.33)	2 (1.63)	1 (0.97)
Flank pain						
No	9131 (88.8)	7310 (87.8)	1821 (93.2)	1670 (94.7)	97 (78.9)	87 (84.5)
Yes	922 (8.97)	820 (9.85)	102 (5.22)	64 (3.63)	25 (20.3)	16 (15.5)
Missing	229 (2.23)	199 (2.39)	30 (1.54)	29 (1.64)	1 (0.81)	0 (0)

LUTS = lower urinary tract symptom; SD = standard deviation; UTI = urinary tract infection.
Percentages are column percentages except in the first row ("Total"), which are row percentages. Individual cancers do not add up to total cancers as some patients were diagnosed with more than one type of cancer.
Occupational, medication, and travel/environmental risks were considered regardless of time since exposure.
[a] Defined as exposure to dyes, rubber, textiles, and pesticides.
[b] For example, cyclophosphamide and pioglitazone.
[c] Risk of schistosomiasis: relevant exposure to freshwater lakes in Africa, South America, and Middle East.

Table 3 – Final prediction model for urinary tract cancer using mixed effects multivariable logistic regression

Variable	Coefficient	Odds ratio	95% Confidence interval	*p* value
Nonvisible haematuria		1.00		
Visible haematuria	1.99	7.29	5.24–10.1	<0.001
Female		1.00		
Male	0.69	2.00	1.40–2.87	<0.001
Age (yr)	0.07	1.07	1.06–1.09	<0.001
Age per 5-yr difference	0.15	1.17	1.10–1.23	<0.001
Never smoker		1.00		
Ex-smoker	0.70	2.02	1.74–2.34	<0.001
Current smoker	1.06	2.88	2.44–3.41	<0.001
Family history of urothelial cancer				
No		1.00		
Yes	0.72	2.06	1.39–3.03	0.001
Previous benign haematuria investigation				
No		1.00		
Yes	−0.84	0.43	0.34–0.55	<0.001
UTI history				
None		1.00		
Single	−0.74	0.48	0.38–0.60	<0.001

Table 3 (*continued*)

Variable	Coefficient	Odds ratio	95% Confidence interval	*p* value
Recurrent	−0.75	0.47	0.36–0.62	<0.001
Catheter use				
No		1.00		
Yes	−1.57	0.21	0.14–0.31	<0.001
Pelvic radiotherapy history				
No		1.00		
Yes	−0.59	0.56	0.35–0.88	0.013
Anticoagulation				
No		1.00		
Yes	−0.17	0.84	0.70–1.01	0.060
Dysuria/suprapubic pain				
No		1.00		
Yes	−0.32	0.72	0.61–0.86	<0.001
Interaction terms				
Visible haematuria & male	−0.82	0.44	0.30–0.65	<0.001
Visible haematuria & age	−0.02	0.98	0.96–0.99	0.007
Age & anticoagulation	−0.02	0.98	0.97–1.00	0.007
Intercept	−2.79			
Intercountry variance	0.84		0.40–1.78	
Intercentre variance	0.35		0.25–0.56	
Intraclass correlation for country	0.19		0.10–0.33	
Intraclass correlation for centre	0.26		0.17–0.38	

AUC = area under the curve for receiver operating characteristics; CI = confidence interval; UTI = Urinary tract infection.
Number of observations in model = 9464 (92.0% of cohort); missing data = 818 (8.0%); number of events = 1863/9464 (19.7%); number of country groups = 26 with a mean of 364 observations per group (minimum = 30, maximum = 4294); number of centre groups = 110 with a mean of 85.3 observations per group (minimum = 36, maximum = 611). Age has been centred about its mean. Performance in predicting all urinary tract cancers in cohort: AUC = 0.86 (95% CI 0.85–0.87).

Table 4 – Validation of the predictive model for urinary tract cancer: AUC of different countries

Country	AUC
UK	0.80
France	0.78
Italy	0.75
Spain	0.75
USA	0.84
Canada	0.77
Ireland	0.85
Portugal	0.81
Turkey	0.78
China	0.89

AUC = area under the curve for receiver operating characteristics.

the model on different countries showed good performance, with an AUC of at least 0.75 (Italy and Spain) to 0.89 (China; Table 4).

3.3. Risk calculator

The predicted risk was calculated from the risk score, which is derived from the linear coefficients as follows:

Risk score = Intercept + 0.07 * (age − mean age) + 0.69 * (male) + 1.99 * (visible haematuria) + 1.06 * (smoker) + 0.70 * (ex-smoker) + 0.72 * (family history of urothelial cancer) − 0.84 * (previous benign haematuria investigation) − 0.74 * (single episode of UTI) − 0.75 * (recurrent episodes of UTI) − 1.57 * (catheter use) − 0.59 * (pelvic radiotherapy history) − 0.17 * (anticoagulation) − 0.32 * (dysuria) − 0.82 * (sex * visible haematuria) − 0.02 * (visible haematuria * [age − mean age]) − 0.02 * (anticoagulation * [age − mean age])

which relates to an individual's probability of urinary tract cancer as follows:

Patient's individual risk of urinary tract cancer = $1/1 + \text{exponential}^{-(\textbf{Risk Score})}$

where age is a continuous variable in years, and all other variables are assigned a value of 0 if absent and a value of 1 if present.

As an example of its use, a 70-yr-old man with visible haematuria who is a current smoker has a predicted risk of 51.7% and would be classified to have a high risk. Conversely, a 40-yr-old woman with a single urinary tract infection (UTI) associated with visible haematuria has a predicted risk of 4.0% and would be classified to have a low risk.

When stratified by risk groups, the majority of patients (over 80%) from our cohort were stratified into intermediate- and high-risk groups (Table 5), which also had the largest proportion of cancers (Supplementary Fig. 2). Within the very-low-, low-, intermediate-, and high-risk groups from our cohort, the cancer prevalence was 0.82%, 3.90%, 10.5%, and 30.5%, respectively.

4. Discussion

Our principal finding in this analysis was the development of a clinically relevant and practical prediction model for urinary tract cancer, with good discrimination, which can support clinicians in prioritising the investigation of patients with haematuria. This is the first model developed using a broad international cohort and was designed to investigate a number of clinically important risk markers commonly proposed to be associated with cancer detection. The final predictors of increased risk of cancer in our model were visible haematuria, older age, current or ex-smoker history, family history of urothelial cancer, and male sex. Predictors associated with a decreased risk of cancer in

Table 5 – Stratification of observed cancers by risk categories

	Very low risk	Low risk	Intermediate risk	High risk	Total
Number of patients, *n* (row %)	366 (3.56)	1411 (13.7)	3318 (32.3)	5187 (50.5)	10 282
Cancer prevalence, *n* (column %)	3 (0.82)	55 (3.90)	349 (10.5)	1581 (30.5)	1988[a]
Bladder cancer, *n*	2	45	314	1401	1762
UTUC cancer, *n*	0	2	11	110	123
Renal cancer, *n*	1	8	24	70	103

UTUC = upper tract urothelial cancer.
[a] Some patients had more than one type of cancer, so the total sum is higher than the number of patients with cancer.

the model were previous benign haematuria investigations, UTIs associated with the haematuria presentation, dysuria or suprapubic pain, anticoagulation, catheter use, and previous pelvic radiotherapy.

The study was specifically designed to include a wide variety of risk markers associated with urinary tract cancer in patients with haematuria. Another strength of the study includes its large cohort size (with a large number of events per predictor), which is important for a multivariable analysis especially with rarer cancers. The relatively higher cancer prevalence than that reported in previous studies has been explained further in the prevalence analysis and is due to adjustment of confounders and a more representative, larger, international population sample [4]. Furthermore, results are generalisable within secondary care given the diversity of the cohort, as it is the first multinational study on patients with haematuria. The adjustment for geographical effects within the model takes into consideration the heterogeneity in the background risk of different countries.

Our model improves on an existing predictive model [9] by including upper tract cancers and a wider variety of markers, whilst being consistent with the association of visible haematuria, male sex, age, and smoking with bladder cancer. Another difference between models is the use of a risk threshold for investigation versus risk stratification of all referred patients. By using a risk threshold over which patients should be investigated, cancers may be missed if their predicted risk is below this threshold. By applying it to our cohort, 53/1953 (2.71%) of all urinary tract cancers would be missed. Conversely, our model uses risk stratification and so considers all referred patients for investigation.

Some risk markers in our model showed a decreased risk of cancer, likely because their presence is a sign of benign causes of haematuria rather than malignant disease. In patients with UTIs and haematuria, prior studies did not find a difference in the cancer risk between these patients and a control group [7,16]. The association of pelvic radiotherapy with bladder cancer has mainly been shown in selected patients with prostate cancer comparing radiotherapy with radical surgery [14,22], not in patients presenting with haematuria. Similarly, evidence showing the association of catheter use with bladder cancer is limited and demonstrated in a selected population without haematuria [23]. Our study population is therefore different, and our analysis suggests that these markers are more likely associated with benign disease such as cystitis [24].

It has been reported that the most common cause for haematuria admissions to hospital among patients on an oral anticoagulant is benign disease (21%), followed by urothelial carcinoma (17%) [15]. This may explain its effect in our model as it was generally associated with a reduced risk of cancer, except in older patients due to its interaction with age. We included anticoagulation as a predictor in the final model even though it was not statistically significant for urinary tract cancers ($p = 0.06$), due to its clinical importance and common use in patients with haematuria.

The main limitation of the prediction model is that it excludes patients with a prior history of urological malignancy or without haematuria, and it should not be applied to such patients. Furthermore, one significant predictor (flank pain) was excluded from the final model for urinary tract cancer following clinical judgement, as upper tract cancers are much rarer than bladder cancer in patients with haematuria. In addition, flank pain is commonly associated with benign pathology such as urolithiasis. However, we suggest that the model may be modified to upstage patients' risk category if they had flank pain and haematuria. Secondly, although we conducted thorough internal validation, we were unable to perform external validation on a separate dataset as, to our knowledge, such an extensive dataset of predictors in patients referred to secondary care has not been published or made available.

After external validation, we envisage the typical use of our predictive model, as an online calculator, by urologists in a "haematuria clinic" setting to prioritise and triage patients referred to them with any type of haematuria based on the overall risk of urinary tract cancer. We would also recommend this tool to be used to prompt a shared decision-making process between the clinician and the patient regarding their individual risks and to guide the urgency and necessity of investigations. Though we have set thresholds for risk stratification, clinicians may use their own judgement of risk based on the patients' individual predicted risks of cancer. These thresholds were also the most voted thresholds for use in a Twitter poll by urologists [25]. The threshold of <1% for very-low-risk cancer was chosen as this is less than the risk of infection in patients undergoing a flexible cystoscopy [26]. Therefore, avoidance of investigation in these patients may be considered. Prioritising high-risk patients for early investigation and detection of urinary tract cancer are important for reducing morbidity and mortality, and for prioritising the use of limited resources. Similarly, avoiding or delaying investigation in very-low-risk patients and choosing a less invasive or lower urgency investigative approach in low-risk patients may improve patient experience and resource burden.

Additional research to build on this analysis should include external validation of the model and assessment of its use in a clinical trial evaluating a new diagnostic path-

way for patients referred with haematuria. Further recommendations for the clinical implication and type of investigation required in each risk category, especially with regard to imaging and cytology, require diagnostic test evaluation and will be the subject of future analysis from the IDENTIFY study.

5. Conclusions

We present a risk prediction model for the detection of urinary tract cancer based on a large international cohort of patients presenting with haematuria in secondary care. It can be used in secondary care for risk stratification and to aid the shared decision-making process between clinicians and patients for any further investigation. This could have a major impact on healthcare resource usage.

***Author contributions*:** Sinan Khadhouri had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: All listed authors and collaborators.
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Appendix A. Supplementary data

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References

[1] Mathew A, Desai K. An audit of urology two-week wait referrals in a large teaching hospital in England. Ann R Coll Surg Engl 2009;91:310.
[2] Hawary AM, Warburton HE, Brough RJ, et al. The "2-week wait" rule for referrals for suspected urological cancers—urgent need for refinement of criteria. Ann R Coll Surg Engl 2008;90:517–22.
[3] Tan WS, Feber A, Sarpong R, et al. Who should be investigated for haematuria? Results of a contemporary prospective observational study of 3556 patients. Eur Urol 2018;74:10–4.
[4] Khadhouri S, Gallagher KM, MacKenzie KR, et al. The IDENTIFY study: the investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer; a multicentre observational study. BJU Int 2021;128:440–50.
[5] Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53.
[6] Wong MCS, Fung FDH, Leung C, Cheung WWL, Goggins WB, Ng CF. The global epidemiology of bladder cancer: a joinpoint regression analysis of its incidence and mortality trends and projection. Sci Rep 2018;8:1129.
[7] Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000;163:524–7.
[8] Rodgers MA, Hempel S, Aho T, Kelly JD, Kleijnen J, Westwood M. Diagnostic tests used in the investigation of adult haematuria: a systematic review. BJU Int 2006;98:1154–60.
[9] Tan WS, Ahmad A, Feber A, et al. Development and validation of a haematuria cancer risk score to identify patients at risk of harbouring cancer. J Intern Med 2019;285:436–45.
[10] Edwards TJ, Dickinson AJ, Natale S, Gosling J, McGrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU Int 2006;97:301–5.
[11] Dobruch J, Daneshmand S, Fisch M, et al. Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. Eur Urol 2016;69:300–10.
[12] Brennan P, Bogillot O, Cordier S, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. Int J Cancer 2000;86:289–94.
[13] Schmidt-Hansen M, Berendse S, Hamilton W. The association between symptoms and bladder or renal tract cancer in primary care: a systematic review. Br J Gen Pract 2015;65:e769–75.
[14] Moschini M, Zaffuto E, Karakiewicz PI, et al. External beam radiotherapy increases the risk of bladder cancer when compared with radical prostatectomy in patients affected by prostate cancer: a population-based analysis. Eur Urol 2019;75:319–28.
[15] Satasivam P, Reeves F, Lin M, et al. The effect of oral anticoagulation on the prevalence and management of haematuria in a contemporary Australian patient cohort. BJU Int 2012;110(Suppl 4):80–4.
[16] Summerton N, Mann S, Rigby AS, Ashley J, Palmer S, Hetherington JW. Patients with new onset haematuria: assessing the discriminant value of clinical information in relation to urological malignancies. Br J Gen Pract 2002;52:284–9.
[17] Khadhouri S, Gallagher KM, MacKenzie K, et al. IDENTIFY: The investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer: a multicentre cohort study. Int J Surg Protoc 2020;21:8–12.
[18] Moons KGM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1–W73.

[19] Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. Eur Urol 2016;70:93–105.
[20] Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—part B: prostate and bladder tumours. Eur Urol 2016;70:106–19.
[21] Ensor J, Snell KI, Martin EC. PMCALPLOT: Stata module to produce calibration plot of prediction model performance. Statistical Software Components 2020.
[22] Zhao S, Xie Q, Yang R, et al. High prevalence of secondary bladder cancer in men on radiotherapy for prostate cancer: evidence from a meta-analysis. Cancer Manag Res 2019;11:587–98.
[23] Ho CH, Sung KC, Lim SW, et al. Chronic indwelling urinary catheter increase the risk of bladder cancer, even in patients without spinal cord injury. Medicine (Baltimore) 2015;94:e1736.
[24] Gurka MK, Chen LN, Bhagat A, et al. Hematuria following stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer. Radiat Oncol 2015;10:44.
[25] BJU International. For a patient with haematuria referred to you for suspected urinary tract cancer, what risk thresholds would you use to classify them as very low, low, intermediate or high risk? 2021. https://TwitterCom/BJUIjournal/Status/1453448682746044425.
[26] Trail M, Cullen J, Fulton E, et al. Evaluating the safety of performing flexible cystoscopy when urinalysis suggests presence of "infection": results of a prospective clinical study in 2350 patients. Eur Urol Open Sci 2021:3128–36.