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Risk prediction models for symptomatic patients with bladder and kidney cancer: a systematic review

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Abstract

Background
Timely diagnosis of bladder and kidney cancer is key to improving clinical outcomes. Given the challenges of early diagnosis, models incorporating clinical symptoms and signs may be helpful to primary care clinicians when triaging at risk patients.

Aim
This review identifies and compares published models that use clinical signs and symptoms to predict the risk of undiagnosed prevalent kidney or bladder cancer.

Method
A search identified primary research reporting or validating models predicting the risk of bladder or kidney cancer in Medline and EMBASE. After screening identified studies for inclusion, we extracted data onto a standardised form. The risk models were classified using TRIPOD guidelines and evaluated using the PROBAST assessment tool.

Results
The search identified 20,661 articles. Twenty studies (29 models) were identified through screening. All the models included haematuria (visible, non-visible or unspecified), and seven included additional signs and symptoms (such as abdominal pain). The models combined clinical features with other factors (including demographic factors and urinary biomarkers) to predict the risk of undiagnosed prevalent cancer. Most models (n=24) had acceptable-to-good discrimination (AUROC>0.7), however, only six have been externally validated. All of the studies had either high or unclear risk of bias (RoB).

Conclusion
Models were identified that could be used in primary care to guide referrals, with potential to identify lower risk patients with visible haematuria and to stratify individuals who present with non-visible haematuria. However, before application in general practise external validations in appropriate populations are required.

Keywords
Bladder Cancer; Kidney Cancer; Risk Prediction; Early Diagnosis; Systematic Review

How this fits in
Timely diagnosis of kidney and bladder cancer from primary care is key to improving survival rates, but remains challenging. Risk models have been suggested as a possible tool to guide clinicians in making referral decisions, particularly in individuals who present atypically. This systematic review identifies a number of models that may be of interest, in particular, models able to identify low risk individuals who may not require referral and a model suitable for stratifying risk in individuals with NVH. However, only a small number of models include clinical features other than haematuria and there is a lack of external validations.
Background and Aims

Bladder and kidney cancer are the 9th and 15th most common cancers worldwide. In the United Kingdom (UK), bladder and kidney cancers each account for approximately 3% of new cancer cases, and 5300 and 4500 annual deaths, with their incidence expected to rise [1, 2]. Early stage diagnosis is strongly correlated with improved survival rates for both bladder and kidney cancer [1, 2].

The majority of bladder and kidney cancers (75% and 59% respectively) are diagnosed following a referral from primary care in the UK [1-3]. A prolonged primary care interval (from patient presentation to referral) is associated with worse clinical outcomes [4, 5]. Currently, in England, median diagnosis time for bladder and kidney cancer - after presentation in primary care with a relevant clinical feature - is 51 and 70 days respectively, with variation seen by symptom [6]. Visible haematuria is present in the majority of patients with bladder cancer (53%), however, it is less common in individuals diagnosed with kidney cancer (18%) [7]. Currently, the National Institute for Health and Care Excellence (NICE) guidelines advise urgent referral for suspected bladder or kidney cancer for unexplained non-visible haematuria (NVH) or persistent visible haematuria (VH) in all individuals aged 60 and 45 years respectively [8]. While 5.1% of people with VH in a primary care setting are ultimately diagnosed with urological cancers, the positive predictive value (PPV) of NVH is less certain and may be as low as 1.6% in primary care [7]. The focus on haematuria may impede early identification of cancers that present atypically or with a number of non-specific symptoms [6, 9]. This could also lead to the over-referral of lower risk individuals presenting with haematuria [10].

Risk assessment tools have the potential to improve timely diagnosis of cancer by combining multiple clinical features to identify symptomatic patients who would benefit from early referral and reducing investigations in individuals least likely to benefit [7, 11]. Risk models to guide clinical decision-making are becoming more common. For example, QCancer tool, which estimates the risk of 11 cancers based on symptoms and patient characteristics, has been integrated into primary care software [12]. Although not routinely used to aid referral decisions for suspected cancer, risk assessment tools have been identified as a potential method for improving UK cancer outcomes [13].

In this review, we systematically identified and compared published models that incorporate symptoms and signs (referred to as clinical features) and estimate the risk of undiagnosed prevalent bladder or kidney cancer at an individual level. The review focuses on the risk factors included in the models, the performance of the models (discrimination and calibration) and their potential use in primary care.

Method

We performed a systematic review following an a priori established study protocol (PROSPERO ID:CRD42018116967).

An electronic literature search of Medline and EMBASE was performed in November 2018 and updated in December 2020. We included literature published 1980-2020, using a combination of subject headings incorporating “bladder/renal/kidney/urinary-tract cancer”, “risk/risk factor/chance” and “model/prediction/score” (supplementary materials).

We included studies that fulfil all of the following criteria:

i. Are published, peer reviewed, primary research
ii. Present a model, which here is considered the use of a combination of two or more factors to identify individuals with a higher risk of undiagnosed prevalent bladder or kidney cancer. Studies predicting recurrent or future risk were excluded.

iii. Incorporate at least one clinical feature as a risk factor

iv. Include at least one quantitative measure of model performance (discrimination, calibration or accuracy). Accepted measures include (but are not limited to) AUROC, \( R^2 \) (goodness of fit), sensitivity, specificity, PPV and NPV. Graphical measures alone were not accepted.

v. Are applicable to the general population. Studies including only specific groups - for example, individuals receiving dialysis - were excluded.

One reviewer carried out the search. Reviewers screened titles and abstracts to exclude clearly irrelevant papers. Pilot screening was carried out to ensure consistency between reviewers. The full text was examined, by two reviewers, if a definite decision to exclude could not be made based on the title and abstract alone. Disagreements were resolved by discussion with a third reviewer.

Data extraction was carried out independently by two reviewers for all included studies. Where studies included multiple different models all were included separately. Details of model development, validation and performance were extracted into a standardised form. Included studies were classified according to the TRIPOD guidelines [14]. The PROBAST tool was used to assess risk of bias (RoB) over four domains of interest (population, risk factors, outcomes and analysis) [15, 16]. Information required for this assessment was extracted by two reviewers, and one reviewer scored the studies. A second reviewer checked the RoB assessment process.

Results

After duplicates were removed, the search identified 20,661 papers. Of these, 19,959 were excluded by title and abstract screening and 686 after full-text assessment. We identified 20 studies, describing 29 models, which satisfied the inclusion criteria [10, 17-35] (Fig.1).

Study design and setting

Of the 20 studies, 16 were cohort studies [10, 17, 19-30, 33, 34] and four were case-control studies [18, 31, 32, 35] (Table:S1). Six studies were performed in a UK primary care setting, using routinely coded data [22-24, 31, 32, 35]. Nine were conducted in secondary (or specialist) care settings, including hospital outpatient clinics and urology departments [10, 18, 21, 26-28, 30, 33, 34]. The remaining five studies do not provide enough information about the study setting to be classified as primary or secondary [17, 19, 20, 25, 29] (for example, referring to recruitment at a “clinic”).

Most studies included European (n=11) or North American populations (n=8); two studies were based in South-East Asia [21, 26]. The six studies in a primary care setting included a mixture of asymptomatic and symptomatic individuals [22-24, 31, 32, 35]. Eleven studies included patients undergoing investigation for haematuria [10, 18-21, 26, 27, 30, 33, 34], in some cases restricted to NVH (n=2) [27, 34] or painless haematuria (n=4) [18-20, 26]. Three studies included individuals classified as high-risk based on a prior history of haematuria [30] or smoking status [17, 29]. One study included all individuals enrolled on a health insurance plan who underwent urinalysis [25].

Of the 29 models (Table:1), the outcomes were a diagnosis of bladder cancer (n=19) [17-21, 29, 32-35], kidney cancer (n=1) [31] or urological cancer (n=9) (bladder and kidney cancer, either with [10, 22, 25] or without [23, 24, 27, 28] cancers of the urothelium). Most were developed in mixed-sex populations, although a small number were developed specifically for men (n=2) [22, 23] and
women (n=2) [22, 24]. The majority of the models were developed using logistic regression (n=22), although other methodologies, including survival models (n=2), were also found.

Internal validation – either bootstrapping [17-20] or split-sampling (random [22-24, 34] or non-random [28, 29]) – has been carried out for 22 models. Only eight models have been externally validated [10, 25, 27, 28].

**Risk Factors**

Haematuria was included as a risk factor in all of the included models (Table:S2). However, there was significant variation in the type of haematuria included. Four models used only VH [22, 31, 32], four only NVH [25, 28, 34] and fourteen included both (as separate risk factors (n=2) [25, 35] or the degree of haematuria was used as a risk factor (n=12) [18-21, 29, 33]). In seven models, the type of haematuria was unspecified [17, 23, 24].

Most studies (n=14) reported the association between haematuria and the outcome of interest (Table:S4). Frequently the presence of haematuria, either any (n=3), visible (n=5) or non-visible (n=2), was compared to no haematuria. One study reported the odds ratio (OR) separately for both VH (26, 95%CI: 22-30) and NVH (20, 95%CI:12-33) for bladder cancer [35]. Four studies, developed in cohorts composed of individuals undergoing investigation for haematuria for suspected bladder cancer, gave ORs for individuals with VH compared to those with NVH [18, 20, 21, 33]. All showed stronger associations with VH than NVH (1.71-3.85 in multivariate analysis).

Seven models included other clinical features in addition to haematuria [22-24, 31, 32, 35]. These included abdominal pain (n=7), weight loss (n=4), anaemia (n=3), loss of appetite (n=3), urinary tract infection (UTI) (n=3) and dysuria (n=3). In each case, the risk due to haematuria was at least 8 times higher than the risk from all other clinical features.

Demographic risk factors, including age (n=27), sex (n=20) and race (n=9), were used in most models. Modifiable lifestyle risk factors, including smoking (n=24) and BMI (n=2), were also considered. Three models included abnormal blood tests [31, 32]; eight urine biomarkers [17, 18, 20, 29] and seven urine cytology [17, 18, 20, 29].

**Risk of Bias**

Most of the 20 studies included in this systematic review were assessed to have a high RoB (n=17) in both development and validation (Fig.2). The most common issues were seen in domain 4 (analysis) in which 12/15 development studies and 8/12 validation studies were at high RoB. This was frequently due to an insufficient number of cases or incomplete reporting of performance measures (including not reporting calibration of model).

**Performance Measures**

Discrimination (the area under the receiver-operating curve (AUROC)) was reported for 26 models (Fig.3 and Table:S3). Calibration was reported for 13 internal [20, 22-24, 29, 34] and three external validations [21, 30, 33].

The four Hippisley-Cox models, developed in unfiltered population-based cohorts to predict urological cancer, all have AUROC values in the range 0.88-0.96 in a large internal validation (Fig.2, group:D) [22-24]. These models report good calibration and relatively high levels of accuracy (sensitivity:0.77-0.71, specificity:0.90-0.91) when using the 90th percentile of risk as a cut-off. They also have high negative predictive values (NPV=100%), for positive predictive values (PPVs) in the range 0.6-1.6% for this threshold. The two models developed for men have slightly higher
discrimination than those for women. Demographic and lifestyle risk factors are combined with clinical features - smoking, haematuria and abdominal pain feature in all four. Two specified visible haematuria as a symptom, the other two did not specify type of haematuria. This did not significantly affect performance; however, other risk factors also differed between these models.

The models by Shephard and Price predicted the risk of developing kidney [31] and bladder [32, 35] cancer by combining pairs of symptoms observed in unfiltered population-based cohorts. The combinations of symptoms with the highest accuracy were microcytosis and abdominal pain for kidney cancer (PPV>5%), and VH and raised white blood cell count for bladder cancer (PPV=8.8%). It is shown [35] that even in older age groups (>60), the PPV of NVH for bladder cancer is low (0.8%), however, when combined with dysuria, for example, this increases to 4.5%. These symptom combinations are rare (<10 cases out of 3140 in development population), so may have limited impact individually.

The model developed by Matulewicz [34] was developed in a population with newly diagnosed NVH and had an AUROC value of 0.74 (95% CI: 0.67-0.80) in an internal validation (Fig.2, group:A). This model combines a categorical measurement of NVH (RBC/hpf) with age, sex, smoking and race to predict likelihood of a bladder cancer diagnosis. For threshold (>5% risk), which gives PPV=11.6%, reasonable accuracy (sensitivity:68%, specificity:75%) and a high NPV (98%) are demonstrated.

The remaining 20 models report discrimination in populations undergoing investigation for suspected urological cancer, with varying proportions of the populations having VH and NVH (Fig.2, groups:B and C). On average, discrimination is higher in models developed only in individuals with haematuria (group:B) and in models that incorporate urinary biomarkers. The model with highest discrimination in external validation was Tan2019 [33] (AUROC=0.77). This model combines type of haematuria with age, sex and smoking status to predict the risk of a bladder cancer diagnosis. For an optimised cut-off point (>4.015%), the reported accuracy measures indicate high sensitivity (0.99) can be achieved, however, the corresponding specificity was low (0.31). The best performing models incorporating urinary biomarkers are Cha2012c and Cha2012d [19] (AUROC=0.9 in internal validation). The degree of haematuria (VH or NVH) is combined with the uCyt assay (an immunocytochemical test which detects markers from malignant urothelial cells in urine [36]) and several demographic and lifestyle factors. Cha2012d also included the results of cytology as a risk factor; this does not seem to improve model performance. The models by Loo [28] include an indication of the severity of NVH (>25 RBC/hpf), Loo2013b has high discrimination (AUROC=0.809) in external validation [27].

Discussion

Summary

Our review found thirteen risk prediction models with good discrimination (>0.8) for urological cancer. All of the models included haematuria and seven incorporated additional clinical signs or symptoms. Most were developed in populations undergoing investigation for suspected urological cancer, with only seven developed in primary care (or unfiltered population-based) cohorts. Only eight of the identified models have been externally validated and around half (n=14) have no reported measure of calibration.

Strengths and limitations

This is the first study we are aware of to provide a systematic and up-to-date review of the existing risk prediction models for bladder or kidney cancer with application to primary care. The study
benefits from a comprehensive search and rigorous screening of studies for inclusion. 29 models were identified in this process, providing a clear overview of the current research in this area. We used the PROBAST tool, a new quality assessment tool for risk prediction models, to perform a robust assessment of the RoB for each model and identify areas where the quality of research is low.

We were unable to perform a meta-analysis due to the heterogeneity in the study designs, including differences in study type (development and validation), design (cohort and case-control), setting (primary and secondary care) and recruitment criteria. A further limitation is that several models used coded information from primary care records and may be subject to bias in clinician recording and choice of investigations.

Comparison to Existing Literature

Recent reviews have examined risk assessment tools for the identification of other undiagnosed cancers, including colorectal [37] and ovarian cancer [38]. The models identified by those studies had similar discriminative ability to those described in this review. As in this review, a lack of high quality studies and external validations was noted. There was a wider range of models developed specifically for primary care settings for those cancers, than we identified for urological cancer.

Although VH has been widely shown to be associated with urological cancer [39], the association with other clinical factors (including NVH and UTIs) is poorly understood [7, 39], with variation between different populations [40]. In this review, only seven models included clinical factors other than haematuria and only five studies directly compared VH and NVH as risk factors. Additionally, haematuria has a much higher contribution than other clinical risk factors in all models where more than one is used.

Implications

The seven models developed in primary care settings [22-24, 31, 32, 35] are the most applicable to this review question. The excellent performance of the four Hippisley-Cox models, if replicated in an external validation, would make them suitable for use in primary care, in particular, they may enable clinicians to identify lower risk individuals who do not need referral. However, it is unclear how these models would be used and how this would compare to current practice. For example, we cannot infer if any individuals currently eligible for referral (such as those with VH) would be reclassified using these models.

The model developed by Matulewicz [34], in a population with newly identified NVH, could be used in primary care to guide referral decisions in individuals with NVH. Current guidelines for referral for suspected urological cancer in the UK differentiate between types of haematuria (VH and NVH) and age (>45 and >60 respectively). There is concern that lower risk patients, such as younger individuals with NVH, are not managed optimally [7]. The Matulewicz model, by combining a categorical measure of NVH with demographic factors, identifies both high and low risk individuals successfully (PPV:10.4% and NPV:98.2%). This suggests that this model could identify some individuals with NVH who are aged <60 years who would benefit from referral and some aged >60 years who are at lower risk and do not need referral. The high PPVs seen when using this model, and when NVH was combined with other clinical signs in the study by Price [35], indicates the need to consider the broader clinical context when making referral decisions in patients with NVH.

Conclusions and Future Research

Haematuria was the strongest clinical risk factor associated with urological cancers and was included in all of the models identified. Several models have been developed in primary care populations that
could be used to guide referrals, in particular, identifying those at lower risk least likely to benefit from further investigation. Additionally, one model was identified which could be used to stratify the risk of cancer in individuals presenting with NVH.

Future research in this area should initially focus on carrying out external validations of the identified models in a suitable primary care cohort. Researchers should then consider the impact that implementing these models to support referral decisions would have on both patient outcomes and the healthcare service in their analyses.

**Figure Captions**

Fig. 1 – PRISMA flow diagram

Fig. 3 – Model discrimination, area under the receiver-operating curve (AUROC). Models are split into groups describing the development population and within each group ordered by the number of risk factors used. Study type (development, internal and external validation), type of haematuria used in model and study setting are indicated on the plot.

Fig. 2 - Risk of Bias (RoB) assessment using PROBAST framework. For each study, RoB is shown for model development and validation separately. RoB is assessed over four domains (D1: population, D2: risk factors, D3: outcome, D4: analysis), the overall results for each study are shown on the right.

Table 1 – Summary of included models

Table S1 – The included studies: details of study setting and study population are given. TRIPOD classification and results of the RoB assessment are also indicated.

Table S2 – The included models. Details of the intended outcome of the model (a subsequent diagnosis of kidney, bladder or ureter cancer) and the included risk factors are given.

Table S3 – The reported performance measures of the models (discrimination, calibration and accuracy) are given separately for development, internal validation and external validation.

Table S4 – Measured associations (ORs) between haematuria and urological cancers in the included studies

Table S5 – MEDLINE Search Strategy

Table S6 – EMBASE Search Strategy

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Ethical Approval
Not applicable

Availability of Materials
Templates of data extraction forms and code used to produce graphs are not publically available, but will be provided upon contacting corresponding author

References


Figure 1. PRISMA flow diagram
Figure 2. Risk of Bias (RoB) assessment using PROBAST framework. For each study, RoB is shown for model development and validation separately. RoB is assessed over four domains (D1: population, D2: risk factors, D3: outcome, D4: analysis), the overall results for each study are shown on the right.
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<td>Tan2019</td>
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<td>Georgieva2019</td>
<td>BCa, BCa, UCa</td>
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<tr>
<td>Matulewicz2020</td>
<td>BCa</td>
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</tbody>
</table>

| χ | BCa – bladder cancer, KCa – kidney cancer, UCa – cancer of the ureter, *VH – visible (gross) haematuria, NVH – non-visible (microscopic) haematuria, degree – VH or NVH, †None – development only, Int – at least internally validated, Ext – externally validated |