SIUJ Société Internationale d'Urologie Journal

Article

Evaluation of Cxbladder Compared to the Conventional Workup of Haematuria to Exclude a Diagnosis of Urothelial Carcinoma

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Abstract

Background/Objectives: Haematuria is a common presenting symptom of Urothelial Carcinoma (UC). Traditionally, the "triple workup"—comprising flexible cystoscopy, voided urine cytology and upper tract imaging is used as the standard diagnostic approach for evaluating these patients. However, these investigations can be invasive, time-consuming, and costly. Cxbladder, a urine based genomic biomarker, utilises a non-invasive, singular urine sample to calculate probability of UC based on a patient's risk factors and gene expression. The aim of Cxbladder is to establish patients with a high probability of no UC being present, which suggests that the traditional investigations are not required. This study evaluates the performance of Cxbladder Triage compared to the standard triple workup in patients presenting with haematuria, excluding a diagnosis of UC. **Methods**: A prospective, observational study was conducted at a single Australian tertiary hospital. A total of 258 patients, who presented with haematuria from 2020 to 2023, underwent both a Cxbladder Triage test and standard triple workup, comprising three urine cytology samples, imaging and a flexible cystoscopy. Some patients required either a bladder biopsy or tumour resection to further diagnose and treat a suspected UC. Diagnostic accuracy was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the proportion of missed tumours. **Results**: Overall, 5.4% of patients, presenting with haematuria were diagnosed with UC (n = 14). Cxbladder Triage demonstrated a sensitivity of 92.9% (95% confidence interval [CI]: 66.0–99.8) and an NPV of 92.9% (95% CI: 66.0–99.8). This was higher than cytology alone, which recorded a sensitivity of 42.9% (CI 9.9–81.6%) and NPV of 78.9% (95% CI: 54.4–94.0) for the detection of UC. When cytology and imaging were combined to investigate UC, the sensitivity and NPV recorded were 75.0% (95% CI: 42.8–94.5) and 80.0% (95% CI: 51.9–95.8), respectively. The proportion of UC cases missed by Cxbladder Triage was 6.7% (n = 1). **Conclusions**: In our cohort of patients presenting with haematuria, Cxbladder Triage offers a non-invasive alternative to the traditional workup for the detection of UC, with both a high sensitivity and NPV. Cxbladder Triage offers an alternative diagnostic workup for low-risk patients, which has the potential to reduce unnecessary invasive tests, procedures, and cost to the healthcare system.

Keywords: Cxbladder; urothelial carcinoma; bladder cancer; haematuria

Academic Editor: Sanjay Sinha

Received: 22 August 2025
Revised: 11 December 2025
Accepted: 22 December 2025
Published: 11 February 2026

1. Introduction

Urothelial Carcinoma (UC) can affect any body surface where urothelium is present. It is often divided into three categories, depending on the location it affects: bladder cancer (BC), upper tract UC (UTUC) and urethral carcinoma. BC accounts for 90–95% of all UC, with UTUC the next most common (5–10%), followed by urethral carcinoma (1%) [1]. BC is the tenth most common cancer diagnosed worldwide when accounted for sex and has an incidence rate of 9.5 in men and 2.4 in women (per 100,000 person/years) [2]. The mortality rate for BC, when standardised for age, is 3.3 in men and 0.86 in women (per 100,000 person/years) [2].

One of the most common presenting symptoms for UC is haematuria and when visible haematuria (VH) is present it is associated with a higher stage of disease upon diagnosis, compared to nonvisible haematuria [3]. When suspecting a diagnosis of UC, a thorough history and physical examination should be undertaken along with upper tract imaging. Computed tomography urography (CTU) is commonly performed to detect any filling defects and/or hydronephrosis, which may represent the presence of UC [4,5]. Although, when BC is diagnosed, the incidence of UTUC on baseline CTU is low (1.8%), leading some to question its utility [6–8]. When BC is located near the trigone, the incidence of UTUC on baseline imaging increases to 7.5% [7].

The gold standard for diagnosis of BC is cystoscopy followed by histopathological diagnosis of any suspicious tissue with a bladder biopsy or transurethral resection of the bladder (TURBT) [9]. However, these procedures are not without risks and is an invasive endoscopy, which requires local and systemic anaesthetic, equipment, theatre time, trained staff and can also cause patient discomfort [10]. Alongside cystoscopy and upper tract imaging, voided urine cytology is used to complete the traditional triple workup of haematuria. Using the Paris System, which was developed in 2022, cytology results are classified as negative for UC, atypical, suspicious for high grade (HG) UC, malignant or inadequate for diagnosis [11]. It is less invasive than other investigations and is useful for the detection of HG UC, with a high specificity at 98% [12,13]. Yet, cytology poses a problem for detecting low grade (LG) UC and carcinoma in situ (CIS) due to its low sensitivity, reported at 40% and between 28–100%, respectively, for LG UC and CIS [13,14]. Lastly, cytology results. which are either atypical or negative, do not exclude the presence of UC, requiring patients to still undergo cystoscopy to further assess [15]. Together, this negates the use of cytology as a standalone diagnostic test and draws attention to other investigations, which could reduce unnecessary and costly procedures.

Subsequently, there has been a focus on the role of non-invasive biomarkers in the diagnostic workup of UC, although none have yet been accepted as routine clinical practice [16]. Ideally, this biomarker has a high sensitivity and high negative predictive value (NPV), which in the workup of haematuria, could be used to exclude a diagnosis of UC. A negative result for the biomarker may also reduce the need for traditional investigations, such as cystoscopy and biopsy and/or resection, if UC can be safely excluded. One of these biomarkers is the Cxbladder test (Pacific Edge Ltd., Dunedin, New Zealand), which measures the concentrations of five genes in a urine sample via a messenger ribonucleic acid (mRNA) test (quantitative reverse transcription polymerase chain reaction) [17,18]. There are different subtypes of this biomarker, which can be used for the evaluation of patients presenting with haematuria (Cxbladder Detect and Cxbladder Triage) and to investigate for a recurrence of UC (Cxbladder Monitor) [19]. This study investigated the utility of Cxbladder Triage, which uses a mathematical equation to calculate a Cxbladder score, representing the probability of UC being present [20]. The score incorporates the level of biomarker expression and a patient's risk factors for UC (age, smoking and gender) [20]. The Cxbladder score is categorised as either having a low probability of UC or requiring further investigation with a standard

workup [18,20]. The aim is to determine patients with a low probability of UC being present, safely excluding the need to undergo further investigations for haematuria workup.

2. Materials and Methods

This study was designed to compare the traditional workup of haematuria to Cxbladder Triage for excluding the diagnosis of UC. A prospective, observational study was performed at a single Australian tertiary hospital and ethics approval was granted by the Western Health Ethics Panel (HREC/19/WH/57718). A total of 258 patients, who presented with haematuria, were consecutively recruited from 2020 to 2023. Inclusion criteria comprised patients $\geq$ 18 years referred for evaluation of haematuria without a previous diagnosis of UC. Exclusion criteria consisted of recent instrumentation of the urinary tract, urinary tract infection (UTI) and/or positive urine culture or ongoing VH. Eligible patients with a positive urine culture and/or symptoms of a UTI were treated with antibiotics before clear urine specimens were obtained for evaluation with cytology and Cxbladder Triage. Patients underwent both a Cxbladder Triage test and the standard workup for haematuria, comprising three urine cytology tests, upper tract imaging (most commonly CTU) and a flexible cystoscopy. For patients that required additional TURBT or bladder biopsy, tissue specimens were categorised as either benign or UC. The stage of UC was classified according to tumour–node–metastasis (TNM) classification, and the grade of UC was determined by the 2004 World Health Organization (WHO)/International Society of Urological Pathology (ISUP) classification system for urothelial neoplasms. Diagnostic accuracy was assessed using sensitivity, specificity, positive predictive value (PPV) and NPV as well as documenting the proportion of missed tumours. Patients recruited were asked to provide a midstream urine (MSU) sample for both urine cytology and Cxbladder Triage tests. These were analysed in the same laboratory at a single tertiary centre. The results of the Cxbladder Triage test were recorded but did not influence clinical management of patients being investigated for haematuria. The traditional triple workup was performed for all patients, regardless of the Cxbladder Triage result.

Descriptive statistics recorded for our patient cohort comprised age, gender and smoking status (pack-years). The number of pack-years was defined as the product of the number of packs of cigarettes smoked per day and duration of time (years smoked). One pack of cigarettes was defined as 20 cigarettes. Cytology, upper tract imaging and Cxbladder Triage results were analysed with sensitivity and NPV for histologically confirmed diagnoses of UC. For comparison of Cxbladder Triage with traditional investigations for haematuria, three cohorts were described. A cohort was each described for patients with either positive or negative Cxbladder Triage and cytology results. An additional cohort was described to include both imaging and cytology results to further compare its utility with the Cxbladder Triage test. For this cohort, a positive result was defined as a positive cytology result or imaging that was suspicious for malignancy. A negative result was defined as a patient having both negative cytology and imaging findings that were not suspicious for malignancy. For simplification of the cytology results, a binary system was employed to classify cytology as either positive or negative. A positive result was defined as either atypical, suspicious or malignant urine cytology. A negative result was defined as negative urine cytology. Similarly, Cxbladder Triage results were classified as either positive or negative. A positive Cxbladder Triage result was defined as a score requiring further investigation to evaluate the presence of UC and a negative result was defined as a score which had a low probability for the presence of UC. For upper tract imaging results, a positive or negative result was determined based on findings suspicious for malignancy. A positive imaging result was defined as the presence of any of the following: mass, filling defect, hydronephrosis or thickening of urothelium or signs of metastasis. A negative result

was defined as the absence of any suspicious findings. Only patients who had cytology, upper tract imaging and Cxbladder Triage results were eligible for analysis and those with incomplete data were excluded.

Statistical analysis was undertaken for patients who met the inclusion criteria as described above. Patient demographics including age and gender were summarised with descriptive statistics. Categorical variables were described using frequencies and percentages. The sensitivity and NPV were calculated using a 95% confidence interval (CI). All analyses were performed using Excel (Microsoft Corporation, Redmond, CA, USA) and SPSS version 30.0 (SPSS Inc., IBM Corp., Armonk, NY, USA).

3. Results

The median age of the study population was 60 years old. In total, 60.1% of patients were male (n = 155) and 39.9% were female (n = 103). Overall, 38.0% of patients had a smoking history of >5 pack years (n = 98). Most patients were investigated for macroscopic haematuria (83.3%, n = 215) and 16.7% (n = 43) presented with microhaematuria. The most common type of upper tract imaging was CTU (n = 256, 99.6%), with only two patients undergoing an ultrasound of the renal tract instead. These patients were younger in age without high-risk features of UC and were presented with microscopic haematuria; 58.1% of patients (n = 150) had a negative Cxbladder Triage result and 38.4% (n = 99) were positive; 3.5% (n = 9) of patients recorded a Cxbladder Triage failure result, which meant a risk stratification for UC could not be generated; 76.0% of patients recorded a negative cytology result (n = 196) and 7.0% (n = 18) were positive; 15.5% of patients (n = 40) did not produce a urine cytology result; 4.3% (n = 11) of patients had suspicious imaging findings for malignancy and 74.4% of patients (n = 192) had unremarkable imaging; 9.7% of patients (n = 25) failed to complete upper tract imaging.

The sensitivity for histologically confirmed UC cases for Cxbladder Triage, cytology alone and combined cytology and imaging results in all patients presenting with haematuria were 92.9% (95% CI: 66.0–99.8), 42.9% (95% CI: 9.9–81.6) and 75.0% (95% CI: 42.8–94.5), respectively. The NPVs for the same groups were, respectively, 92.9% 95% CI: 66.0–99.8), 78.9% (95% CI: 54.4–94.0) and 80.0% (95% CI: 51.9–95.8). Sensitivity and NPV values were also calculated for the subset of patients presenting with microscopic and macroscopic haematuria separately (Table 1).

Table 1. The sensitivity and negative predictive values for histologically confirmed UC cases for Cxbladder Triage, cytology alone and combined cytology and imaging results in patients presenting with haematuria. Separate calculations have been performed for macroscopic and microscopic haematuria. Sensitivity and NPVs are presented as percentages with a 95% CI. UC = urothelial carcinoma; NPV = negative predictive value. CI = confidence interval.

	Cytology		**Cytology/Imaging**		**CxBladder**	
	Sensitivity	**NPV**	**Sensitivity**	**NPV**	**Sensitivity**	**NPV**
Haematuria	42.9% (9.9–81.6)	78.9% (54.4–94.0)	75.0% (42.8–94.5)	80.0% (51.9–95.8)	92.9% (66.0–99.8)	92.9% (66.0–99.8)
Macroscopic haematuria	40.0% (11.9–79.4)	75.0% (47.0–91.7)	77.8% (40.0–97.2)	75.0% (34.9–96.8)	100% (71.5–100.0)	100% (66.4–100.0)
Microscopic Haematuria	66.7% (9.4–99.2)	85.7% (42.1–99.6)	66.7% (9.4–99.2)	85.7% (42.1–99.6)	66.7% (9.4–99.2)	80.0% (28.4–99.5)

Patients who required further investigation for UC underwent additional procedures with either a bladder biopsy or TURBT. No upper tract tumours were identified in this population on CTU. Occasionally, cystoscopy revealed other causes for haematuria, for which

clinicians recommended alternative procedures, such as transurethral resection of the prostate (TURP), video urodynamic studies (VUDS) or cystolithopaxy. Most patients (82.5%, *n* = 212) did not require any further investigation after an unremarkable cystoscopy. From the study population, 51 patients underwent an additional procedure and 5.4% of patients (*n* = 14) were diagnosed with UC. 1 patient had carcinoma in situ (CIS), 4 with LG UC and 9 with HG UC. A total of 29 patients that underwent an additional procedure had a benign tissue result with no evidence of UC. Then, 1 patient was diagnosed with prostatic adenocarcinoma invading into the bladder and 1 patient was recommended to undergo a TURBT based on cystoscopic examination but declined surgery. Further classification of patients diagnosed with UC can be visualised in the chart (Figure 1) and the different types of additional procedures performed can be seen in the table below (Figure 2). The frequency of patients diagnosed with UC based on investigations for haematuria is described below in Figure 3.

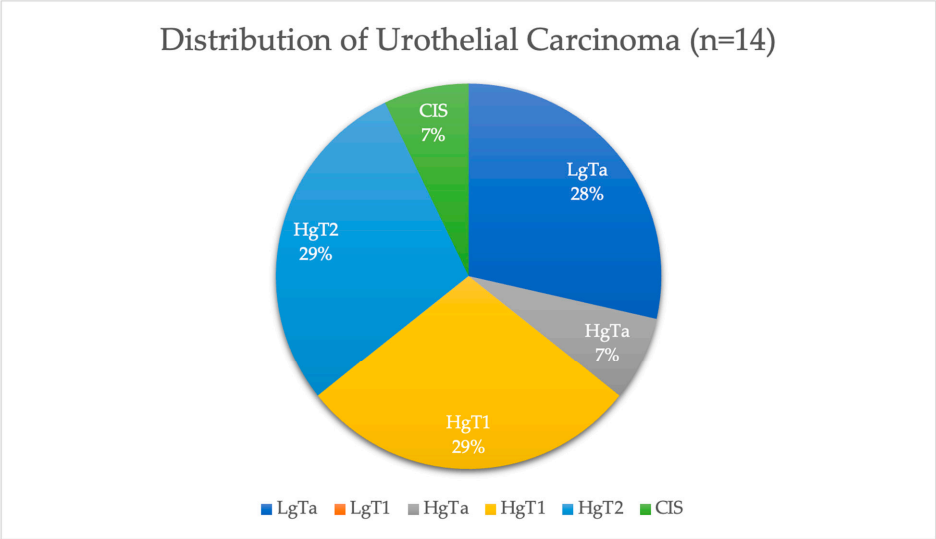

Figure 1. Classification of UC as per the 2004 World Health Organization (WHO)/International Society of Urological Pathology (ISUP) classification system for urothelial neoplasms. LgTa = low grade non-invasive UC; LgT1 = low grade UC with lamina propria invasion; HgTa = high grade non-invasive UC; HgT1 = low grade UC with lamina propria invasion; HgT2 = high grade UC with muscularis propria invasion; CIS = carcinoma in situ; UC = Urothelial Carcinoma.

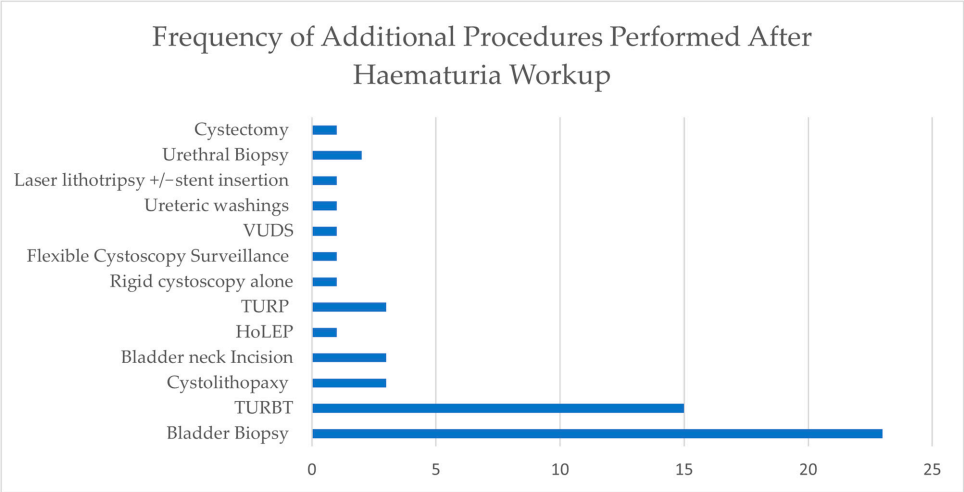

Figure 2. The distribution of additional procedures performed following the standard triple workup for haematuria. VUDS = video urodynamic studies; TURP = transurethral resection of the prostate; HoLEP = Holmium Laser Enucleation of the Prostate; TURBT = transurethral resection of bladder tumour.

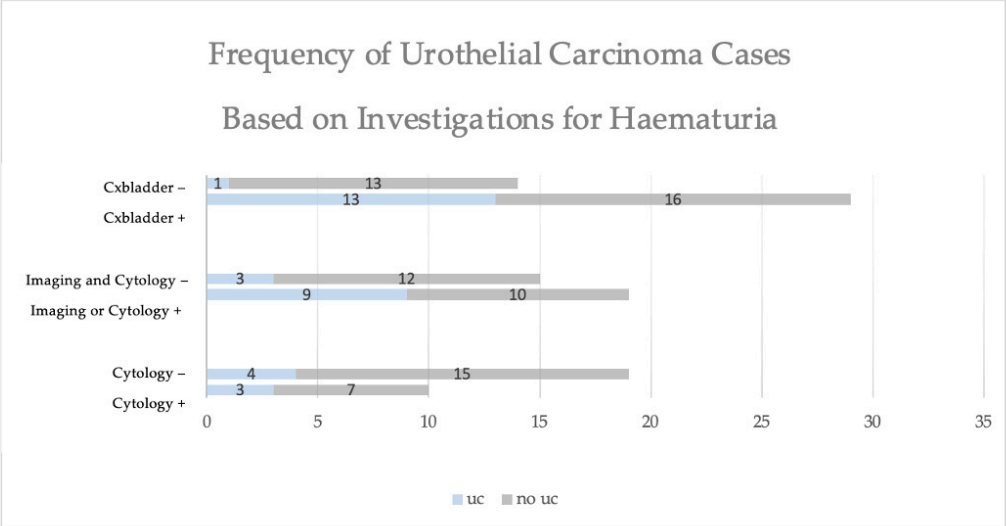

Figure 3. The frequency of positive and negative results for Cxbladder Triage, cytology alone and combined cytology and imaging results, compared with the frequency of histologically confirmed UC cases. UC = Urothelial Carcinoma.

4. Discussion

Our study found that Cxbladder performed better than both cytology alone as well as cytology and imaging combined, in excluding a diagnosis of UC. This was demonstrated by the Cxbladder test recording a higher NPV (92.9%, 95% CI: 66.0–99.8) and sensitivity (92.9%, 95% CI: 66.0–99.8). This shows the utility of Cxbladder as a good rule-out test for UC. Our findings are in keeping with those in the literature, including a multicentre analysis of patients presenting with haematuria in Australasia (n = 485), which found a high sensitivity for CxBladder (81.8%) in the detection of UC, as compared to cytology (56%, 95% CI: 48.3, 68.3) [20]. However, cytology had high specificity (94.5%, 95% CI: 91.9, 96.5), which underscores the trade-off between sensitivity and specificity that exists for molecular tests.

Cxbladder also has downstream benefits for reducing invasive tests, and thus, reduce the burden on healthcare systems. This concept was emphasised by Darling et al. [21], which evaluated whether Cxbladder Triage and Detect modalities impacted the number of investigations originally recommended for patients presenting with microscopic haematuria (n = 33). This study analysed 792 decision points in the haematuria workup of 12 urologists and demonstrated that the addition of Cxbladder test results reduced the number of cystoscopies and CTU performed by 44% and 20%, respectively [21]. Additionally, Cxbladder has demonstrated cost-effectiveness for implementation into clinical pathways for patients presenting with haematuria and BC surveillance. In an Australian study, which evaluated the use of CxMonitor for BC surveillance instead of cystoscopy (n = 98), there was a reduction of 850 Australian Dollars (AUD) for each cystoscopy avoided and an overall savings of AUD 78,200 [22].

A downside of cytology is that interpretation of results is user dependent and an experienced cytopathologist is needed to improve accuracy [23]. Yet even if an experienced pathologist is utilised, there is still a high rate of false-negative results for urine cytology [23]. In our study, urine cytology missed 57.1% (n = 4) of UC cases but Cxbladder only missed 7.14% (n = 1). In the DETECT 1 study that recruited patients referred for haematuria investigation across 40 hospitals in England, 567 patients underwent urine cytology, and there was a total of 21 BC and 5 UTUC cases missed [24]. Of the cases missed in this study, 19% (n = 4) were ≥pT2 and 38% of all missed cases were high-risk UC [24]. The sensitivity of cytology in the DETECT 1 study was also low at 43.5% but did improve to 90.2% when analysing patients with either suspicious imaging CTU results for UC or positive urine

cytology [24]. In our cohort, when cytology was combined with imaging studies, there was an increase in sensitivity (75.0%, 95% CI: 42.8–94.5) and NPV (80.0%, 95% CI: 51.9–95.8), but 25% (n = 3) of UC cases were missed. The only patient in our study diagnosed with UC was missed by Cxbladder and also not correctly identified by cytology or imaging. Together, we see that cytology will likely miss a proportion of muscle invasive BC and/or high-risk UC. Yet, when combined with other modalities, such as CTU, the sensitivity of detection of UC increases drastically, underlining cytology's role as an adjunct in the workup of haematuria.

On the other hand, the current position of the European Association of Urology (EAU) guidelines on urinary biomarkers recommends their use only as adjuncts to cystoscopy rather than standalone diagnostic tests for UC [9]. In our cohort, we found that Cxbladder is excellent for excluding patients that do not have UC, with the specificity and PPV of the test remaining low at 55.2% and 44.8%, respectively. This area continues to be an area of active research with other biomarkers, such as CellDetect and UroVysion, which show promise in the primary detection of UC and like Cxbladder, have demonstrated superior sensitivity and NPV results compared to cytology [21]. These other biomarkers do however tend to also sacrifice specificity for increased sensitivity [11]. Other biomarkers have subsequently been developed to improve on this limitation including Xpert®-BC-Detection (Cepheid, Sunnyvale, CA, USA) and the Bladder EpiCheck test (Nucleix, Rehovot, Israel). For comparison, Xpert®-BC-Detection, which evaluates five mRNA targets linked to BC, has been shown to have both high sensitivity (90%) and NPV (98%) in a prospective study of 156 patients presenting with haematuria [25]. The Bladder EpiCheck test instead analyses fifteen different methylation biomarkers to generate an EpiScore and determine the likelihood of an underlying UC being present [26,27]. This test has been evaluated in a review by Mancini et al. [28] of eight prospective cohort studies (n = 1993), highlighting a sensitivity of detecting all grades of UC between 62.3 and 90% and a high NPV of 89.4–97.4%.

The trade-off between sensitivity and specificity is reflected in our study results, which found that cytology had a higher specificity (68.2%) compared with Cxbladder (55.2%). Together, we see the utility of the Cxbladder Triage test as an adjunct to cystoscopy in the primary detection of UC for patients presenting with haematuria, which has been shown to outperform cytology alone and cytology combined with imaging.

One limitation of this study was that the cytology results were not interpreted by the same cytopathologist, which can lead to some variation in results. Cytology reporting depends on the individual reporting, and a high level of experience can improve accuracy [23]. Additionally, positive voided urine samples included atypical cytology given that a portion of these patients may be diagnosed with UC [29]. Atypical cytology can also result from benign conditions such as stone disease or inflammation, yet it is important to not exclude cases, which may represent underlying malignancy. With a larger sample size, future studies could restrict classification of a "positive" group to only include suspicious or positive results for cytology. Without these constraints, the specificity of cytology for diagnosis of UC may artificially deflated and the superiority of Cxbladder overemphasised. Further limitations of this study include its monocentric design and small number of confirmed cases of UC (n = 14), which limit its statistical power. Lastly, there was no cost-effectiveness analysis performed to evaluate Cxbladder Triage in our health service. This may also be useful to produce in future research to optimise the haematuria referral pathway.

5. Conclusions

In our study, Cxbladder Triage demonstrated a high diagnostic accuracy in excluding low-risk patients who do not have UC. It offers a potential non-invasive alternative to reduce unnecessary invasive procedures for the workup of haematuria. Future studies that incorpo-

rate a larger number of UC cases in a multicentric design may provide deeper insight into the utility of Cxbladder Triage when compared with the traditional evaluation of haematuria.

Author Contributions: Conceptualization, H.Z. and S.K.; methodology, H.Z. and S.K.; software, H.L. and S.W.; validation, H.Z., S.K. and H.L.; formal analysis, H.L.; investigation, H.L.; resources, H.L.; data curation, S.W., S.K. and H.L.; writing—original draft preparation, H.L.; writing—review and editing, H.L., B.D., D.H., N.M.C., S.K. and H.Z.; visualisation, H.Z.; supervision, N.M.C. and H.Z.; project administration, N.M.C.; funding acquisition, N.M.C. and H.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Pacific Edge Ltd. (Dunedin, New Zealand). $10,000 AUD was provided to enable part-time employment for data collection and management of study materials. $1000 AUD per month was provided for ongoing nurse support and to mail out forms to patients. In addition, funding was given to Western Health for transportation of samples of Cxbladder from study subjects to the pathology provider during the study.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Western Health Ethics Panel (HREC/19/WH/57718) on 3 April 2020.

Informed Consent Statement: Each patient provided written informed consent for involvement in the study.

Data Availability Statement: The full dataset is available under motivated reasonable request to the corresponding author.

Conflicts of Interest: All authors certify that Pacific Edge Ltd. funded this research but had no influence on the subject matter discussed in the manuscript. No other conflicts of interest are declared.

Abbreviations

The following abbreviations are used in this manuscript:

UC	Urothelial Carcinoma
BC	Bladder Cancer
PPV	Positive Predictive Value
NPV	Negative Predictive Value
UTUC	Upper Tract Urothelial Carcinoma
VH	Visible Haematuria
CTU	Computed Tomography Urography
TURBT	Transurethral Resection of Bladder Tumour
HG	High Grade
LG	Low Grade
CIS	Carcinoma in situ
mRNA	Messenger Ribonucleic Acid
Ltd	Limited Company
MSU	Midstream Urine
WHO	World Health Organisation
ISUP	International Society of Urological Pathology
TURP	Transurethral Resection of the Prostate
VUDS	Video Urodynamic Studies
LgTa	Low Grade Non-Invasive Urothelial Carcinoma
LgT1	Low Grade Urothelial Carcinoma with Lamina Propria Invasion
HgTa	High Grade Non-Invasive Urothelial Carcinoma
HgT1	High Grade Urothelial Carcinoma with Lamina Propria Invasion
HgT2	High Grade Muscle Invasive Urothelial Carcinoma
HoLEP	Holmium Laser Enucleation of the Prostate
CI	Confidence Interval
EAU	European Association of Urology

References

1. Leslie, S.W.; Soon-Sutton, T.L.; Aeddula, N.R. Bladder Cancer. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
2. International Agency for Research on Cancer. *Estimated Number of New Cases in 2020, Worldwide, Both Sexes, All Ages*; World Health Organization: Geneva, Switzerland, 2021.
3. Ramirez, D.; Gupta, A.; Canter, D.; Harrow, B.; Dobbs, R.W.; Kucherov, V.; Mueller, E.; Streeper, N.; Uhlman, M.A.; Svatek, R.S.; et al. Microscopic haematuria at time of diagnosis is associated with lower disease stage in patients with newly diagnosed bladder cancer. *BJU Int.* **2015**, *117*, 783–786. [CrossRef]
4. Trinh, T.W.; Glazer, D.I.; Sadow, C.A.; Sahni, V.A.; Geller, N.L.; Silverman, S.G. Bladder cancer diagnosis with CT urography: Test characteristics and reasons for false-positive and false-negative results. *Abdom. Radiol.* **2018**, *43*, 663–671. [CrossRef]
5. Waisbrod, S.; Natsos, A.; Wettstein, M.S.; Saba, K.; Hermanns, T.; Fankhauser, C.D.; Müller, A. Assessment of diagnostic yield of cystoscopy and computed tomographic urography for urinary tract cancers in patients evaluated for microhematuria: A systematic review and meta-analysis. *JAMA Netw. Open* **2021**, *4*, e218409. [CrossRef]
6. Goessl, C.; Knispel, H.H.; Miller, K.; Klan, R. Is routine excretory urography necessary at first diagnosis of bladder cancer? *J. Urol.* **1997**, *157*, 480. [CrossRef]
7. Palou, J.; Rodríguez-Rubio, F.; Huguet, J.; Segarra, J.; Ribal, M.J.; Alcaraz, A.; Villavicencio, H. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. *J. Urol.* **2005**, *174*, 859–861. [CrossRef]
8. Holmang, S.; Hedelin, H.; Anderström, C.; Holmberg, E.; Johansson, S.L. Long-term follow-up of a bladder carcinoma cohort: Routine follow-up urography is not necessary. *J. Urol.* **1998**, *160*, 45. [CrossRef]
9. European Association of Urology. *EAU Guidelines on Non-Muscle-Invasive Bladder Cancer (TaT1 and CIS)—2023 Update*; EAU Guidelines Office: Arnhem, The Netherlands, 2023. Available online: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/chapter/diagnosis (accessed on 29 June 2025).
10. Sanli, O.; Dobruch, J.; Knowles, M.A.; Burger, M.; Alemozaffar, M.; Nielsen, M.E.; Lotan, Y. Bladder cancer. *Nat. Rev. Dis. Primers* **2017**, *3*, 17022. [CrossRef] [PubMed]
11. Wojcik, E.M.; Kurtycz, D.F.I.; Rosenthal, D.L. *The Paris System for Reporting Urinary Cytology*, 2nd ed.; Springer: Cham, Switzerland, 2022.
12. DeGeorge, K.C.; Holt, H.R.; Hodges, S.C. Bladder cancer: Diagnosis and treatment. *Am. Fam. Physician* **2017**, *96*, 507–514.
13. Blick, C.G.; Nazir, S.A.; Mallett, S.; Turney, B.W.; Onwu, N.N.; Roberts, I.S.; Crew, J.P.; Cowan, N.C. Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: Results for 778 patients from a hospital haematuria clinic. *BJU Int.* **2011**, *110*, 84–94. [CrossRef] [PubMed]
14. Têtu, B. Diagnosis of urothelial carcinoma from urine. *Mod. Pathol.* **2009**, *22*, S53–S59. [CrossRef] [PubMed]
15. VandenBussche, C.J.; Allison, D.B.; Gupta, M.; Ali, S.Z.; Rosenthal, D.L. A 20-year and 46,000-specimen journey to Paris reveals the influence of reporting systems and passive peer feedback on pathologist practice patterns. *Cancer Cytopathol.* **2018**, *126*, 381–389. [CrossRef]
16. Soria, F.; Droller, M.J.; Lotan, Y.; Gontero, P.; D'Andrea, D.; Gust, K.M.; Rouprêt, M.; Babjuk, M.; Palou, J.; Shariat, S.F. An up-to-date catalog of available urinary biomarkers for the surveillance of non-muscle invasive bladder cancer. *World J. Urol.* **2018**, *36*, 1981–1995. [CrossRef]
17. Kavalieris, L.; O'sullivan, P.; Frampton, C.; Guilford, P.; Darling, D.; Jacobson, E.; Suttie, J.; Raman, J.D.; Shariat, S.F.; Lotan, Y. Performance Characteristics of a Multigene Urine Biomarker Test for Monitoring for Recurrent Urothelial Carcinoma in a Multicenter Study. *J. Urol.* **2017**, *197*, 1419–1426. [CrossRef] [PubMed]
18. Kavalieris, L.; O'Sullivan, P.J.; Suttie, J.M.; Pownall, B.K.; Gilling, P.J.; Chemasle, C.; Darling, D.G. A segregation index combining phenotypic (clinical characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma. *BMC Urol.* **2015**, *15*, 23. [CrossRef]
19. Harvey, J.C.; Cambridge, L.M.; Ellen, C.W.; Colonval, M.; Hazlett, J.A.; Newell, J.; Zhou, X.; Guilford, P.J. Analytical Validation of Cxbladder® Detect, Triage, and Monitor: Assays for Detection and Management of Urothelial Carcinoma. *Diagnostics* **2024**, *14*, 2061. [CrossRef]
20. O'Sullivan, P.; Sharples, K.; Dalphin, M.; Davidson, P.; Gilling, P.; Cambridge, L.; Harvey, J.; Toro, T.; Giles, N.; Luxmanan, C.; et al. A Multigene Urine Test for the Detection and Stratification of Bladder Cancer in Patients Presenting with Hematuria. *J. Urol.* **2012**, *188*, 741–747. [CrossRef]
21. Darling, D.; Luxmanan, C.; O'Sullivan, P.; Lough, T.; Suttie, J. Clinical Utility of Cxbladder for the Diagnosis of Urothelial Carcinoma. *Adv. Ther.* **2017**, *34*, 1087–1096. [CrossRef] [PubMed]
22. Guduguntla, A.; Whish-Wilson, T.; Chandler, L.; Gyomber, D. A novel bladder cancer surveillance schedule using bladder Cx for patients on annual surveillance. *BJUI Compass* **2025**, *6*, e468. [CrossRef]
23. Tian, W.; Shore, K.T.; Shah, R.B. Significant reduction of indeterminate (atypical) diagnosis after implementation of The Paris System for Reporting Urinary Cytology: A single-institution study of more than 27,000 cases. *Cancer Cytopathol.* **2020**, *129*, 114–120. [CrossRef] [PubMed]

24. Tan, W.S.; Sarpong, R.; Khetrapal, P.; Rodney, S.; Mostafid, H.; Cresswell, J.; Watson, D.; Rane, A.; Hicks, J.; Hellawell, G.; et al. Does Urinary Cytology Have a Role in Haematuria Investigations? *BJU Int.* **2019**, *123*, 74–81. [CrossRef]
25. Kavcic, N.; Peric, I.; Zagorac, A.; Vokac, N.K. Clinical Evaluation of Two Non-Invasive Genetic Tests for Detection and Monitoring of Urothelial Carcinoma: Validation of UroVysion and Xpert Bladder Cancer Detection Test. *Front. Genet.* **2022**, *13*, 839598. [CrossRef] [PubMed]
26. Pierconti, F.; Rossi, E.D.; Cenci, T.; Carlino, A.; Fiorentino, V.; Totaro, A.; Sacco, E.; Palermo, G.; Iacovelli, R.; Larocca, L.M.; et al. DNA methylation analysis in urinary samples: A useful method to predict the risk of neoplastic recurrence in patients with urothelial carcinoma of the bladder in the high-risk group. *Cancer Cytopathol.* **2022**, *131*, 158–164. [CrossRef] [PubMed]
27. Shang, D.; Liu, Y.; Xu, X.; Chen, Z.; Wang, D. Diagnostic value comparison of CellDetect, fluorescent in situ hybridization (FISH), and cytology in urothelial carcinoma. *Cancer Cell Int.* **2021**, *21*, 465. [CrossRef] [PubMed]
28. Mancini, M.; Righetto, M.; Zumerle, S.; Montopoli, M.; Zattoni, F. The Bladder EpiCheck Test as a Non-Invasive Tool Based on the Identification of DNA Methylation in Bladder Cancer Cells in the Urine: A Review of Published Evidence. *Int. J. Mol. Sci.* **2020**, *21*, 6542. [CrossRef]
29. Mokhtar, G.; Al-Dousari, M.; Al-Ghamedi, D. Diagnostic significance of atypical category in the voided urine samples: A retrospective study in a tertiary care center. *Urol. Ann.* **2010**, *2*, 100–106. [CrossRef]