Interference From Haematuria Renders the Urinary BTA Test Not Specific Enough for Diagnosing Bladder Cancer: Evidence From Clinical Practice

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Abstract

Background The urinary bladder tumour antigen (BTA) stat test has already been used for the diagnosis and monitoring of bladder cancer (BC). However, more evidence is needed regarding its efficacy and utility in the clinic. In this study, we investigated the influence of haematuria on the performance of the BTA stat test in a clinical cohort.

Methods Urine samples from 836 subjects, including 50 healthy volunteers, 553 patients with benign urologic disorders, 124 patients with histologically proven BC, and 109 patients with other histologically proven urologic cancers, were analysed by the BTA stat test and urinalysis. We detected the sensitivity and specificity of the BTA stat test in each group, and analysed the effect of haematuria on the specificity.

Results Our data showed that 58.06% of patients had haematuria in the BC group. Haematuria with benign prostatic hyperplasia (BPH), renal hamartoma (RH) and urolithiasis were identified in 39.01%, 42.86% and 66.49% of patients with benign urologic disorders, respectively. Haematuria was identified in 48.72% of prostatic cancer patients and 67.74% of renal cancer patients. The overall sensitivity of the BTA stat test was 90.32%. The sensitivity was 97.22% in BC patients with haematuria and 80.77% in BC patients without haematuria. The overall specificity in healthy individuals, patients with benign urologic disorders and other urologic cancers was 50.84%. In all patients with haematuria, the specificity of the BTA stat test was 15.82%, while it was 72.6% in patients without haematuria.

Conclusions Haematuria has a significant influence on the BTA stat test. Our study suggested that the BTA stat test is not an ideal diagnostic tool for BC.

Background

Bladder cancer (BC) is the ninth most common cancer disease worldwide, and the incidence is particularly high in men [1]. Early BC has a better prognosis, but the progression of the disease greatly increases the rate of metastasis and mortality. The data showed that BC is likely to recur in 50–70% of patients within 5 years [2]. Approximately 15–25% of recurrent BC can be expected to progress to a higher tumour stage [3], and 50% of patients diagnosed with muscle-invasive BC succumb to the disease within five years [4]. Therefore, early screening and long-term close follow-up with repeated examinations are essential.

Currently, cystoscopy and urine cytology are the best tests for the diagnosis of BC [5]. However, there are some limitations in practical clinical applications. Although cystoscopy is the gold standard, it is an invasive test and is not suitable as the first choice for early screening and long-term follow-up. On the other hand, urine cytology has ideal specificity, but its sensitivity varies depending on the grade of the tumour, as urine cytology has low sensitivity in low-grade tumours. In addition, the interpretation of urine cytology results is highly dependent on the skill of the examiner, which varies greatly in different studies and observations [6]. Therefore, finding and evaluating a non-invasive, inexpensive, highly sensitive and specific test for BC is important. Molecular markers have been proposed for the detection of bladder tumours within recent years. However, to be widely used, the specificity and sensitivity of these molecular markers need to be tested more in clinical practice.

The bladder tumour antigen (BTA) stat test is a qualitative enzyme immunoassay that detects a bladder tumour-associated antigen in urine. This antigen has been recognized as a human complement factor H-related protein (hCFHrp) and inhibits the complement pathway to cause cytolysis in cells with a resulting selective advantage for the tumour [7]. Previous studies have suggested that the sensitivity of the BTA stat test is superior to urine cytology, and it has been approved by the US Food and Drug Administration for diagnosing and monitoring of BC [8, 9]. However, the specificity of the BTA stat test is often disturbed by some factors, such as infection and intravesical treatment [10–12]. Few studies have mentioned the impact of haematuria, and relevant clinical data are limited. In the clinic, haematuria is a symptom of BC that cannot be ignored. The initial diagnosis of BC most often occurs after an episode of gross or microscopic haematuria. Over 80% of patients with BC have some degree of haematuria [13, 14]. On the other hand, there are many causes of haematuria other than BC, including many benign urologic disorders. Studies have shown that only 0.7–1.3% of patients with haematuria actually have BC [13, 15–16]. Even between 9 and 18% of normal individuals also have some degree of haematuria [17]. Hence, if haematuria has a serious effect on the specificity of the BTA stat test, using it to screen and monitor for BC can lead to unnecessary investigation and anxiety.

In this study, we analysed the specificity and sensitivity of the BTA stat test in BC. The effect of haematuria on the specificity of the BTA stat test in patients with BC, patients with benign urologic disorders, patients with other urologic cancers and healthy volunteers was also determined. Our study aims to evaluate the utility of the BTA stat test in the diagnosis of BC in clinical practice.

Material And Methods

Patients

We recruited patients with BC, urinary benign diseases and other urinary cancers who visited the Urology Department of the First Affiliated Hospital of Chongqing Medical University from January 2018 to December 2019 (Table 1). Patients enrolled completed related inspections as needed. All diagnoses were confirmed by two urologists. Cystoscopy biopsy was the gold standard for BC diagnosis. Benign diseases of the urinary system were diagnosed according to the corresponding diagnostic criteria. Other urinary cancers were diagnosed based on the results of the corresponding pathological examination. In addition, we recruited a group of healthy volunteers without any clinical evidence of disease. All participants underwent BTA stat test and urinalysis, and none of the participants had mechanical manipulation of the urethra or bladder within the last two weeks before specimen collection. Participants who ultimately did not belong to one of the diagnostic categories or refused further tests to confirm a diagnosis were excluded. Except for the urinary tract infection (UTI) group in the benign urologic disorders group, patients with active UTIs in the other groups, indicated either by symptom reports or by pyuria, were excluded. Except for the urolithiasis group in the benign urologic disorders group, patients with a recent history of urolithiasis in the other groups were excluded.

Table 1
Patient demographics

Group		Total	Male	Female	Mean age	Range age
Bladder cancer		124	103	21	66.7	26−89
Healthy volunteers		50	30	20	50.2	25−72
Benign urologic diseases		553	378	175	62.4	22−95
	BPH	141	141	0	70.7	51−95
	Renal cyst	66	36	30	64.1	47−87
	BAT	75	27	48	53.3	22−74
	RH	28	6	22	55	31−70
	Urolithiasis	185	129	56	60	26−90
	UTI	58	39	19	63.3	48−88
Other urologic cancers		109	101	8	68.9	35−93
	Prostatic cancer	78	78	0	72	52−93
	Renal cancer	31	23	8	61	35−76
BPH, benign prostatic hyperplasia; BAT, benign adrenal tumour; RH, renal hamartoma; UTI, urinary tract infection						

Finally, the study group consisted of 124 patients with BC that was first confirmed histologically. The benign urologic disorders group consisted of benign prostatic hyperplasia (BPH, n = 141), renal cyst (n = 66), benign adrenal tumour (BAT, n = 75), renal hamartoma (RH, n = 28), urolithiasis (n = 185), and UTI (n = 58). The other urologic cancer group consisted of 78 patients with prostate cancer and 31 patients with renal cancer. The healthy volunteers group had 50 individuals.

BTA stat test

The BTA stat test (Polymedco, NY, USA) is a one-step qualitative assay. We assayed all samples according to the manufacturer's instructions [18]. Three drops of urine are placed on the BTA stat test device, which contains a small lateral flow immunochromatographic assay. The urine reacts with colloidal gold-conjugated anti-bladder tumour-associated antigen antibody to form an immune complex. Then, when the immune complex flows through the detection area, it binds to another anti-bladder tumour-associated antigen antibody and forms a visible colour band. If there is no hCFHrp in the urine, no visible line will form in the detection area. Regardless of the presence or absence of hCFHrp in the urine sample, the control area can bind to the detection antibody to form a visible line. Therefore, when both target and control zones form two visible lines, the reading is positive; when only the control line is formed, the reading is negative. The absence of a visible control line means that the test is invalid, and the test needs to be repeated.

Statistical analysis

Statistical analysis was performed using SPSS software, version 20.0 (Chicago, IL, USA). Analysis of the study population characteristics used descriptive statistics. Qualitative variables were expressed as proportions. Sensitivity is defined as the ratio of the number of true positive test results and the number of subjects with confirmed BC. Specificity is defined as the ratio of the number of true-negative test results and the number of subjects without BC. Exact 95% confidence intervals (CIs) indicate the precision of the sensitivity and specificity [8].

Results

BTA stat test in patients with BC

Urinary specimens of 124 patients with histologically proven BC were examined prior to therapy. Histologically, 118 patients had transitional cell carcinoma (TCC), five had squamous cell carcinoma (SCC) and one had undifferentiated carcinoma. Of these patients, 112 patients were BTA-positive, and 12 were BTA-negative with the BTA stat test. According to the histologic stage, 62 patients had a pTa tumour; 24 patients had a pT1 tumour; 28 patients had a pT2 tumour; and 10 patients had a higher tumour (Table 2). The overall sensitivity of the BTA stat test for the detection of BC was 90.32%. The sensitivity of the BTA stat test was 83.87% in pTa tumours, 95.83% in pT1 tumours, and 96.43% in pT2 tumours. None of the patients with pT3-pT4 tumours had negative BTA stat test results. For histologic grades, the sensitivity was 80% for papillary urothelial neoplasm of low malignant potential (PUNLMP) tumours, 70% for low-grade tumours, and 97.75% for high-grade tumours. In the BC group, 72 (58.06%) patients had haematuria. The sensitivity of the BTA stat test was 97.22% for BC patients with haematuria and 80.77% for BC patients without haematuria (Table 2).

Table 2
Sensitivity of the BTA stat test by tumour stage and grade

Variable		Negative	Positive	Total	Sensitivity (%)	95% CI
Bladder cancer		12	112	124	90.32	83.36−94.68
Pathologic subtype						
	TCC	11	107	118 (95.16%)	90.68	83.57−95.02
	SCC	1	4	5 (4.03%)	80	29.88−98.95
	Undifferentiated carcinoma	0	1	1 (0.81%)	100	5.46−100
Grade						
	PUNLMP	1	4	5 (4.03%)	80	29.88−98.95
	Low-grade	9	21	30 (24.19%)	70	50.44−84.59
	High-grade	2	87	89 (71.77%)	97.75	91.35−99.61
Pathologic T stage						
	Ta	10	52	62 (50%)	83.87	71.87−91.59
	T1	1	23	24 (19.35%)	95.83	76.88−99.78
	T2	1	27	28 (22.58%)	96.43	79.76−99.81
	T3	0	4	4 (3.23%)	100	39.57−100
	T4	0	6	6 (4.84%)	100	51.68−100
Urine analysis						
	Positive for RBC	2	70	72 (58.06%)	97.22	89.42−99.52
	Negative for RBC	10	42	52 (41.94%)	80.77	67.03−89.92

TCC, transitional cell carcinoma; SCC, squamous-cell carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; RBC, red blood cell; CI, confidence interval

BTA stat test in healthy volunteers and patients with other urologic disorders

In urinary specimens from 50 healthy individuals, none of the specimens had positive BTA stat test results. Of the 553 patients with benign urologic disorders but without clinical evidence of BC, 262 patients had negative BTA stat test results; in 291 patients, the BTA stat test had false-positive results. The rate of false-positive results varied in correlation with the condition observed: 126 of 185 (68.11%) patients with urolithiasis and 49 of 58 (84.48%) patients with a UTI had false-positive results. A total of 62 of 141 (43.97%) patients with BPH, 28 of 75 (37.33%) patients with BAT and 13 of 28 (46.43%) patients with RH had positive BTA stat test results. In addition, 13 of 66 (19.7%) patients with renal cysts had positive BTA stat test results. Urinary specimens were obtained from 109 patients with other urologic cancers. Of the 78 patients with prostatic cancer, 43 had false-positive BTA stat test results. Of the 31 patients with renal cancer, 16 had false-positive BTA stat test results. The specificity of the BTA stat test for prostatic cancer and renal cancer was 44.87% and 48.39%, respectively. The specificity of the BTA stat test was 100% if only healthy individuals were considered. The overall specificity (healthy individuals, patients with benign urologic disorder and patients with other urologic cancers) of the BTA stat test was 50.84% (Table 3).

Table 3
Specificity of the BTA stat test in 50 healthy subjects and patients in eight disease categories

Category	BTA-negative	BTA-positive	Total	Specificity (%)	95% CI
Healthy volunteers	50	0	50	100	91.11−100
Benign urologic diseases	262	291	553	47.38	43.16−51.63
BPH	79	62	141	56.03	47.43−64.29
Renal cyst	53	13	66	80.3	68.32−88.7
BAT	47	28	75	62.67	50.69−73.34
RH	15	13	28	53.57	34.21−71.99
Urolithiasis	59	126	185	31.89	25.35−39.2
UTI	9	49	58	15.52	7.77−27.93
Other urologic cancers	50	59	109	45.87	36.38−55.66
Prostatic cancer	35	43	78	44.87	33.74−56.51
Renal cancer	15	16	31	48.39	30.56−66.60
Total	362	350	712	50.84	47.11−54.57

BPH, benign prostatic hyperplasia; BAT, benign adrenal tumour; RH, renal hamartoma; UTI, urinary tract infection; CI, confidence interval.

Effect of haematuria on the BTA stat test

In patients with benign urologic disorders, patients with haematuria account for a relatively high proportion. Haematuria in patients with BPH, RH and urolithiasis was 39.01%, 42.86% and 66.48%, respectively. In urologic cancers, 58.06% of BC patients were accompanied by haematuria, and 48.72% of prostatic cancer patients and 67.74% of renal cancer patients were also accompanied by haematuria (Fig. 1). Haematuria had a significant effect on the specificity of the BTA stat test in each group. In benign urologic disorders with haematuria, the false-positive rate of the BTA stat test was 211 of 238 patients, which was significantly higher than that of 80 of 315 patients without haematuria who had the same conditions. The false-positive rate of the BTA stat test increased correspondingly in patients with BPH, RH and urolithiasis, as a high proportion of these patients had haematuria (Fig. 1). The specificity of this test decreased to 8.94%-31.58% in patients with BPH, renal cyst, BAT, RH and urolithiasis associated with haematuria. When we removed the patients with haematuria from this analysis, and the specificity of the BTA stat test increased to 73.21−98.08%. In patients with prostatic cancer and renal cancer, the false-positive rates of the BTA stat test were 43 of 78 and 16 of 31 patients, respectively. In these patients with haematuria, the specificity of the BTA stat test decreased to 28.95% and 42.86%, while the specificity of the BTA stat test in patients with prostatic cancer and renal cancer were both 60% after removing patients with haematuria from this analysis. In all groups of patients with haematuria, the specificity of the BTA stat test was 15.82%, and the overall specificity of the BTA stat test was 70.5% in patients without haematuria (Table 4).

Table 4
Specificity of the BTA stat test in patients with or without haematuria in eight disease categories

Categories	Positive for RBCs					Negative for RBCs				
	Total	BTA-positive	BTA-negative	Specificity (%)	95% CI	Total	BTA-positive	BTA-negative	Specificity (%)	95% CI
Benign urologic diseases	238 (43.04%)	211	27	11.34	7.74–16.24	315 (56.96%)	80	235	74.6	69.35–79.24
BPH	55 (39.01%)	50	5	9.09	3.4-20.71	86 (60.99%)	12	74	86.05	76.50-92.27
Renal cyst	14 (21.21%)	12	2	14.29	2.51–43.85	52 (78.79%)	1	51	98.08	88.42–99.9
BAT	19 (25.33%)	13	6	31.58	13.56–56.50	56 (74.67%)	15	41	73.21	59.46–83.77
RH	12 (42.86%)	10	2	16.67	2.94–49.12	16 (57.14%)	3	13	81.25	53.69–95.03
Urolithiasis	123 (66.49%)	112	11	8.94	4.78–15.49	62 (33.51%)	14	48	77.42	64.72–86.68
UTI	15 (25.86%)	14	1	6.67	0.35–33.97	43 (74.14%)	35	8	18.6	8.92–33.92
Other urologic cancers	59 (54.13%)	39	20	33.9	22.41–47.49	50 (45.87%)	20	30	60	45.2-73.27
Prostate cancer	38 (48.72%)	27	11	28.95	15.99–46.11	40 (51.28%)	16	24	60	43.39–74.72
Renal cancer	21 (67.74%)	12	9	42.86	22.59–65.56	10 (32.26)	4	6	60	27.37–86.31
Total	297 (44.86%)	250	47	15.82	11.96–20.59	365 (55.14)	100	265	72.6	67.67–77.05

BPH, benign prostatic hyperplasia; RH, renal hamartoma; UTI, urinary tract infection; BAT, benign adrenal tumour; CI, confidence inte

Discussion

The high recurrence rate of BC requires long-term regular follow-ups [1]. Non-invasive urine testing is ideal for both the patient and the healthcare system [19]. Among non-invasive urine tests, urine tests with molecular biomarkers are promising tools for diagnosing BC. However, these tests are still not well established in daily clinical routine and in the standard diagnostic workup of BC. Further evaluation of the usefulness of these biomarkers in complex clinical situations is needed before they are recommended for widespread clinical use.

The BTA stat test is a molecular urine test for BC that that is currently subject to the most attention. The BTA stat test specifically recognizes bladder tumour-associated antigen (hCFHrp) in urine through monoclonal antibodies. This antigenic protein is considered to be isolated from the urine of patients with BC but cannot be detected in the urine of most healthy individuals [7]. Previous studies have compared the sensitivity of the BTA stat test and cytology detection in patients with BC diagnosed by cystoscopy, and the sensitivity of the BTA stat test was found to be superior to urine cytology and bladder irrigation cytology [20–22]. However, its effectiveness in real-world clinical situations, especially its specificity under different interference situations, needs further observations. In this study, we investigated the sensitivity and specificity of the BTA stat test in patients who were diagnosed with BC, and more importantly, we investigated the influence of haematuria on the performance of the BTA stat test in a clinical cohort.

Our overall sensitivity results were similar to those published by Dov Pode et al. for the sensitivity of the BTA stat test in detecting bladder tumours [18]. In a European multicentre study of 107 patients with a final diagnosis of BC confirmed by cystoscopy and biopsy, the overall sensitivity of the BTA stat test was 72% [23]. In the Rüdiger Heicappell et al. study, they reported sensitivities for grade I, II, and III disease to be 59.1%, 50%, and 77.3%, respectively [7]. By contrast, we demonstrated higher sensitivities of 80%, 70 and 97.75% for PUNLMP, low-grade and high-grade tumours, respectively. These results may be related to different tumour grading methods. More importantly, our analysis of the overall sensitivity included patients with haematuria, which may show higher sensitivity due to false positives. When patients with haematuria were removed from this analysis, the overall sensitivity of the BTA stat test was 80.77%. If you analyse only patients with

haematuria, the overall sensitivity of the BTA stat test was 97.22%. In our study, the specificity of the BTA stat test was 100% in healthy volunteers, and this result was within the ranges reported by other authors, thus excluding the possibility of technical or analytical errors [10]. Although the specificity of the BTA stat test is high in healthy individuals, disappointing results have nevertheless occurred in patients with other urologic diseases. In a multicentre US study, the specificity of the BTA stat test in patients with BPH, urolithiasis and UTI was 88.5%, 50% and 76%, respectively [24]. These variations may be explained by inherent influencing variables such as infection, trauma, and calculi [10, 23]. Our study showed even lower specificity; the specificity of the BTA stat test decreased to only 31.89% and 15.52% in patients with urolithiasis and UTI, respectively. In patients with prostatic cancer and renal cancer, the specificity of the BTA stat test was only 44.87% and 48.39%, respectively. This may be because we did not exclude patients with haematuria from our total enrolment.

Our results suggested that haematuria leads to high positive rates. On the one hand, the majority of patients with BC will present with haematuria [13, 14]. Considering that hCFHrp is a serum factor, the BTA stat test can possibly concomitantly detect serum proteins that cause haematuria. Another study supports our conclusion; the Makito Miyake group built an experimental haematuria model. They added whole blood to BTA-negative urine samples and found that spiking BTA-negative urine samples with as little as 1 μl whole blood /10 ml urine was enough to produce a positive BTA stat test result [25]. On the other hand, haematuria is the most common symptom in urology patients. In many benign or tumorous urologic diseases, haematuria is often the only manifestation [26]. Even 9–18% of normal individuals also have some degree of haematuria [17]. This fact means that the BTA stat test may be prone to detect particularly high false positives in haematuria patients. We analysed patients with haematuria symptoms in a clinical setting and found that the specificity of the BTA stat test was only 15.82% for all groups of patients with haematuria. The meaning of these data is that when only patients with haematuria symptoms who were suspected of having BC were considered, the specificity of diagnosing BC with the BTA stat test was only 15%. In addition, the proportion of BC patients with haematuria is very small. Previous studies have shown that only 0.7–1.3% of patients with haematuria actually have BC [13, 15, 16]. In this case, if the BTA stat test has such a high false-positive rate for haematuria, it will lack further directivity, and its clinical utility and benefit will be low. The cost of screening includes the cost of labelling each patient and the cost of evaluating patients with false-positive results. Adding any test to the clinical assessment will increase costs; thus, the cost-effectiveness needs to be balanced by the benefits. Optimal screening strategies require identifying a method with high specificity and reasonable sensitivity in a population with significant disease prevalence [27]. The specificity of the marker plays a key role because more patients with false-positive results correlates with needing additional "unnecessary" tests. Our results suggest that the BTA stat test cannot achieve ideal effective specificity and that using it to screen and monitor for BC may lead to "unnecessary" costs. Of course, further studies can compare and analyse the specific costs involved in the clinical practice of qualitative urinary tract testing. However, there are no available data on this problem.

Conclusions

In patients with haematuria, there is a relatively low prevalence of BC. Our research shows that the BTA stat test appears to have a high false-positive rate and low specificity in patients with haematuria. Hence, using the BTA stat test to screen and monitor for BC is not ideal. Our data support the relative inadequacy of the BTA stat test as a diagnostic tool for BC.

Abbreviations

BTA: bladder tumour antigen

BC: bladder cancer

BPH: benign prostatic hyperplasia

RH: renal hamartoma

hCFHrp: human complement factor H-related protein

UTI: urinary tract infection

BAT: benign adrenal tumour

CI: confidence interval

TCC: transitional cell carcinoma

SCC: squamous cell carcinoma

PUNLMP: papillary urothelial neoplasm of low malignant potential

Declarations

Ethics approval and consent to participate

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

XX was involved in data collection and data analysis and wrote the manuscript. WH was involved data collection and edited the manuscript. FY and BX were involved in data collection. All authors reviewed the manuscript.

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Figures
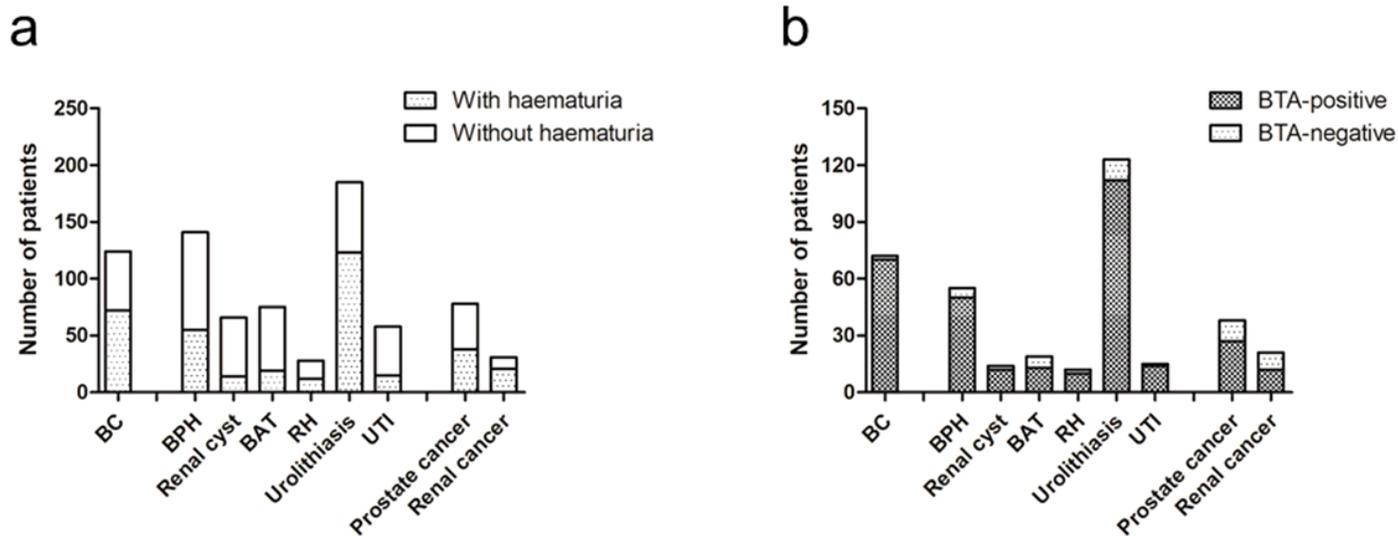
Figure 1

The proportion of haematuria in various diseases and the positive rate of BTA in haematuria patients (Figure1 had uploaded as additional file) Fig. 1 a. The proportion of haematuria in patients with BC, prostatic cancer, renal cancer and benign urologic disorders. Data are from 786 patients. b. The positive rate of BTA in patients with BC, prostatic cancer, renal cancer and benign urologic disorders. Data are from 353 patients.