

Original Research Article

Clinical value of urine nuclear matrix protein 22 (NMP22) quantitative test in the diagnosis of bladder cancer in a schistosoma endemic region

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ABSTRACT

Background: Bladder cancer is the ninth commonest cancer and the 13th most common cause of mortality worldwide. Its early diagnosis poses a great challenge therefore the need to identify biomarkers which may improve the current diagnostic practice.

Methods: This is a prospective study of patients managed for bladder cancer at the urology unit, department of surgery, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria between April 2019 to June 2020. Urine cytology, urine nuclear matrix protein 22 (NMP22) quantitative test and histology of the bladder biopsy specimens were done at the Histopathology and Chemical Pathology laboratory respectively of the Usmanu Danfodiyo University Teaching Hospital, Sokoto. Data was collected using a structured proforma and analyzed using statistical package for social sciences (SPSS) version 20.0.

Results: Eighty-three patients enrolled in the study however 46 of them with features of bladder carcinoma participating in the study group and 37 in the control group. The study and control groups' mean age and age range are (49.70±11.45,18-69) and (51.84±13.75,18-78) years, respectively. The sensitivity, specificity, PPV, NPV and AUC of urine NMP22 and urine cytology in the study were (78.3% vs. 58.7%), (32.4% vs. 100.0%), (59.0% vs. 100.0%), (54.6% vs. 66.1%), (0.207 vs. 0.538) respectively for the diagnosis of bladder cancer.

Conclusions: Urine NMP22 quantitative test shows high sensitivity, low specificity and a low AUC compared to urine cytology and thus of poor clinical value in the diagnosis of bladder cancer in our region.

Keywords: Bladder cancer, Clinical value, Diagnosis, Nuclear matrix protein 22

INTRODUCTION

Bladder cancer is the ninth most common malignancy and ranks thirteenth among the most typical causes of death worldwide.¹ It is the second most common cause of mortality among genito-urinary malignancies, constituting 6% of all male and 2% of female cancers.² Bladder cancer is the second most common malignancy among males and the sixth most common malignancy among females in Sokoto, North-western Nigeria.³

A previous study of bladder cancers in Sokoto revealed 65.1% and 27.9% were SCC and TCC, respectively, with these differences mainly due to schistosomiasis.⁴ Urine cytology and cystoscopy with or without biopsy remain the mainstay for screening, diagnosis, and surveillance in patients with bladder cancer. Urine cytology has a high specificity (90-96%) but lacks sensitivity, especially in low-grade diseases and its effectiveness hinges on the experience of the histopathologist.⁵ Bladder cancer poses a significant burden to patients, families and the

healthcare system; therefore, the need for a simple, accurate, non-invasive means of diagnosing bladder cancer. The improved sensitivity and specificity are equivalent to complement cystoscopy and biopsy in screening, early diagnosis and surveillance.⁶ Several urine markers for the diagnosis of bladder cancer are commercially available with some still investigational.⁷ Amongst these markers, Nuclear Matrix protein 22 (NMP22) test remains a well-researched urinary protein with an advantage due to its availability in a point-of-care format with superior sensitivity to urine cytology for low-grade tumours. The sensitivity and specificity ranged from 47-81% and 67-93%, respectively with its relevance in diagnosis and surveillance.⁷ Its ease of performance and relative cost warranted its choice for our study in a low-resource setting like ours with a heavy burden of bladder cancer.⁸

Objectives

The objective of this study was to determine the specificity, sensitivity, positive and negative predictive values of urine nuclear matrix protein 22 quantitative test in the diagnosis of bladder cancer in a region endemic for schistosomiasis.

METHODS

This is a prospective study conducted on patients presenting at the urology clinic of the Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria between April 2019 and June 2020 with clinical and radiological features of bladder cancer having met the inclusion criteria and consented to participate in the study.

Inclusion criteria

All patients with a clinical and radiological findings of bladder cancer.

Exclusion criteria

Patients who have had radical cystectomy and bowel interposition (urinary diversion), are on immunotherapy-bacilli Calmette of Guerin (BCG) or chemotherapy, with urinary tract infections or on catheter and those with urinary stone disease.

Sample size estimation

The sample size for this study was calculated using Fisher's formula as follows:⁹

$$\eta = Z^2 pq/d^2$$

$$\eta f = \frac{n}{1 + n/N}$$

Where N=63 (number of bladder cancer cases per year in Sokoto),¹⁰ n=desired sample size when study population

is greater than 10,000, n_f =desired sample size when study population is less than 10,000, Z=standard normal deviation=1.96, p=prevalence of bladder cancer(8.7%).¹¹=0.087, q=1- p=0.913 and d=precision or level of significance = 0.05 thus the estimated sample size was 50 subjects/patients.

All patients had a clinical evaluation, urine analysis, urine microscopy, culture and sensitivity, urine cytology, abdominopelvic ultrasound, urine NMP22 ELISA test and eventually urethrocystoscopy and biopsy under caudal block following negative urine culture and prophylactic antibiotics using 1 gram of Ceftriaxone (Avicel®). All patients underwent urethrocystoscopy and biopsy using a rigid cystoscope and video camera assembly, and any visible tumour or suspicious lesions were biopsied. Findings on urethrocystoscopy and biopsy were considered the gold standard and regarded as true positives for comparing the results of the other two tests. Patients with positive isolated NMP22 quantitative test or cytology in the absence of a cystoscopic lesion will be evaluated using a contrast-enhanced computed tomogram to rule out an upper tract lesion or a missed bladder lesion. The visibility of the tumour is essential during urethrocystoscopy; however, flat lesions such as CIS or low-graded tumours could be missed under standard white light cystoscopy. The result was false-positive if there was no tumour; however, the patient will remain on follow-up with a high index of suspicion and re-evaluation every three months with documentation of any lesion that develops. Any lesion in the upper tract or bladder in subsequent cystoscopy is false-positive, assuming a missed lesion. For statistical analysis, chi-square, Fisher's exact, and t-tests were run on Statistical Package for social sciences (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA), and p values less than 0.05 were considered to be indicative of statistical significance. A sterile container was used to collect a urine sample, centrifuged at 20 minutes at a speed of 2000-3000 r.p.m to remove the supernatant. Whenever any supernatant appeared, the urine samples were centrifuged again. Urine specimens stored at -20°C in a refrigerator purchased for the study at the main theatre with avoidance of repeated freeze-thaw cycles were avoided. Nuclear matrix Protein 22 (NMP22) quantitative assay and urine cytology were done six (6) weeks after urethrocystoscopy and biopsy procedure of the bladder for the confirmed cases; however, for the new cases, the urinary NMP22 quantitative test and cytology were done before urethrocystoscopy and biopsy. A single voided urine specimen was collected just before cystoscopy and biopsy; however, two aliquots separated from the sample, one for the NMP22 test and the other for cytology. Nuclear Matrix Protein 22 (NMP22) quantitative test was carried out based on the manufacturer's instruction (PARS BIOCHEM: Cat NO.PRS-01132hu produced by Nanjing Pars Biochem CO., Ltd) in the Chemical pathology laboratory-UDUTH, Sokoto. Two qualified scientists interpreted the NMP22 quantitative test results to allow peer comparison. Urine cytology and histology

were done in the histopathology laboratory of the same hospital. A trained pathologist carried out the voided urine cytology at our institution-cytopathological results classified as malignant, suspicious for malignancy, inconclusive and normal, with the last two negatives.

RESULTS

Eighty-three patients participated in the study, with 46 in the bladder cancer-study group (SG) and 37 in the control

group (CG). The age ranges of SG and CG were 18-69 years and 18-78 years, with mean ages of 49.70±11.45 and 51.84±13.75, respectively. There was no statistically significant difference between the two groups (p=0.441). The male-to-female ratio of 8:1 and 5:1 in the study and the control groups respectively. The most predominant occupation of the patients in the study and control groups was farming in 28 patients (60.9%) and 13 patients (35.1%), respectively. Other socio-demographic characteristics is depicted in (Table 1).

Table 1: Sociodemographic characteristics of the study participants.

Variables	Study group n=46 Frequency (%)	Control group n=37 Frequency (%)	Test statistics	P value
Age (in years)				
18-49	19 (41.3)	14 (37.8)	Fex ² =6.458	0.036
50-69	27 (58.7)	18 (48.6)		
70-above	0 (0.0)	5 (13.5)		
Mean age	49.70±11.45	51.84±13.75		0.441
Sex				
Female	5 (10.9)	6 (16.2)	χ ² =0.510	0.475
Male	41 (89.1)	31 (83.8)		
Marital status				
Married	45 (97.8)	37 (100.0)	χ ² =0.814	0.367
Single	1 (2.2)	0 (0.00)		
Occupation				
Unemployed	6 (13.0)	8 (21.6)	Fex ² =5.838	0.225
Farmer	28 (60.9)	13 (35.1)		
Civil servant	1 (2.2)	2 (5.4)		
Others	3 (6.5)	3 (8.1)		
Business	8 (17.4)	11 (29.7)		
Level of education				
None	42 (91.3)	34 (91.9)	-	-
Secondary	3 (6.5)	1 (2.7)		
Tertiary	1 (2.2)	2 (5.4)		
Address				
Rural	37 (78.3)	27 (73.0)	Fex ² =1.237	0.593
Urban	9 (19.6)	10 (27.0)		

Fex²- Fischer exact test, χ²-Pearson’s Chi-Square test.

In terms of clinical presentation, sixty-five per cent of the patients presented with features of advanced bladder cancer such as bladder mass, weight loss, necroturia and anorexia. Haematuria and LUTS were the most common presentation. Other presentations are depicted in (Table 2). Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) of nuclear matrix protein 22 quantitative test, urine cytology in the diagnosis of bladder cancer. 22 (NMP22) quantitative test and urine cytology in the diagnosis of bladder cancer were determined and reported.

Histopathological types of bladder carcinoma

The most common histopathological type of bladder cancer is SCC, found in 39 patients (85.0%), while TCC in 7 patients (15.0%). These findings and histological grading of bladder cancer are shown below (Table 7).

Two patients (47.8%) had a finding of Schistosoma ova on the histological examination of the tissue specimen.

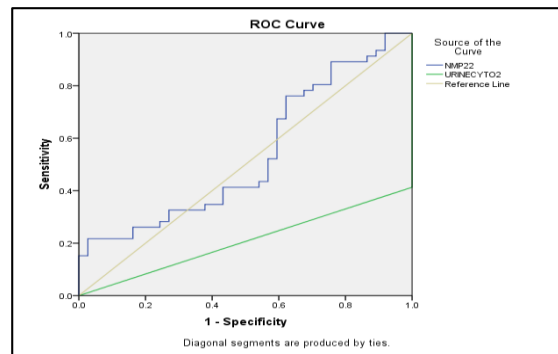


Figure 1: Receiver Operating Characteristics Curve (ROC) for Nuclear Matrix Protein 22 (NMP22) quantitative test and urine cytology in the diagnosis of bladder cancer.

Table 2: Mode of presentation of study (bladder cancer) group.

Variables		Study group N (%)
Haematuria	Yes	45 (97.8)
	No	1 (2.2)
LUTS	Yes	45 (97.8)
	No	1 (2.2)
Necroturia	Yes	32 (69.6)
	No	14 (30.4)
Weight loss	Yes	34 (73.9)
	No	12 (26.1)
Suprapubic swelling	Yes	30 (65.2)
	No	16 (34.8)
Anorexia	Yes	30 (65.2)
	No	16 (34.8)
Drug intake	Yes	2 (4.4)
	No	44 (95.6)
History of schistosomiasis	Yes	34 (73.9)
	No	12 (26.1)
History of smoking	Yes	4 (8.7)
	No	42 (91.3)

Table 3: Computed NMP22 diagnostic test indicators (NMP22 cut-off point of 5.27ng/ml).

NMP22	Bladder cancer	Negative for bladder cancer	Total
Positive ≥ 5.27 (ng/m)	36	25	61
Negative < 5.27 (ng/ml)	10	12	22
Total	46	37	83

Table 4: Computed urine cytology diagnostic test indicators.

Urine cytology	Bladder cancer	Negative for bladder cancer	Total
Positive	27	00	27
Negative	19	37	56
Total	46	37	83

DISCUSSION

The mean age of patients in the study and control groups were 49.70 ± 11.45 and 51.84 ± 13.75 , respectively, with no statistically significant difference between the two groups ($p=0.441$). These findings appear similar to a study by Rambau et al in Tanzania with a mean age of 54 years.¹² This study found that the mean age for urinary bladder cancer diagnosis was 49.7 years regardless of histological type. The younger age of the subjects in this study may also be due to the early age of exposure to the aetiologic agent, which begins in childhood in many of these communities as these children bathe and wade in ponds and participate in farming in bilharzial hyper-endemic areas.^{13,14}

Table 5: Comparison of the diagnostic indicators between NMP22 and urine cytology for bladder cancer detection.

Diagnostic indicators	NMP22 (ng/ml)	Urine cytology
Sensitivity (%)	78.3	58.7
Specificity (%)	32.4	100
Positive predictive value (%)	59	100
Negative predictive value (%)	54.6	66.1
Positive likelihood ratio	1.16	0
Negative likelihood ratio	0.67	0.41
Diagnostic Odds ratio	1.73	0
Diagnostic effectiveness (accuracy) (%)	58	77
Misclassification rate (false positive rate)	42	23
Younden's Index	0.11	0.59

The younger age of incidence of bladder cancer in our study differs from reports from Europe and India, which is due not only to differences in the age of the populations but mainly due to early exposure of our subjects to urinary schistosomiasis, which occurs with high intensity in childhood.¹³⁻¹⁶ Another reason is that haematuria in young patients is considered a natural right-of-passage for maturing adult youngsters.¹⁷ Bladder cancer is generally more common in males than in females, with an overwhelming male preponderance (89.1%), similar to studies by Ochicha et al from Kano.¹⁸ The male prevalence in this study may be explained by the more intense exposure of males in the primary agricultural workforce. Female subjects residing in this region are mainly occupied with household chores with little exposure to the parasite-infested waters except for a few in the deep rural locations who in search of water for drinking and domestic chores wade into streams in order to fetch water.⁴

Most of the patients in the study group (97.8%) presented with haematuria and LUTS, a typical presentation in Schistosoma endemic regions, mainly in younger subjects.² Bowa et al revealed similar findings of haematuria though painful, irritative symptoms, necroturia and bladder mass in patients with mainly SCC from Africa.¹⁹ In the present study, 45.6-69.5% of patients with bladder carcinoma presented with advanced disease features, including bladder mass, necroturia, weight loss, and anorexia, apart from the common denominator of haematuria and LUTS. Our patients presented with advanced disease for several reasons proffered. These reasons include ignorance, poor access to specialist care, and the common occurrence of painless gross haematuria in these schistosoma-endemic locations, thus it's occurrence in the young subjects. The scenario mentioned above differs from the situation in the western world, where the above debilitating conditions do not

exist; the presence of gross haematuria being regarded as a probable harbinger of serious urological malignancy resulting in early presentation to the hospital

necessitating early diagnosis of superficial, non-muscle-invasive disease which has good prognosis.²⁰

Table 6: Area under the curve for both NMP22 and urine cytology.

Test result variable(s)	Area	Standard error ^a	Asymptotic significance	Asymptotic 95% confidence interval	
				Lower bond	Upper bond
Urine NMP22	0.538	0.065	0.552	0.411	0.665
Urine cytology	0.207	0.05	0.000	0.109	0.304

a. Under the nonparametric assumption, b. Null hypothesis: true area=0.5.

Also, the squamous cell variety of bladder cancer that results from a background of chronic urinary schistosomiasis presents with invasive muscle disease due to inflammatory and fibrotic processes associated with schistosoma induced-bladder cancer pathogenesis.^{21,22}

Table 7: Histopathological types and grades of bladder carcinoma.

Histological type	Frequency (%) n=46	Grade
Squamous cell carcinoma	39 (85)	I 4 (8.7)
		II 24 (52.3)
		III 11 (24.0)
Transitional cell carcinoma	7 (15)	I 2 (4.3)
		II 0 (0.0)
		III 5 (10.7)
Total	46	46

In the present study, the sensitivity and specificity of Nuclear matrix protein 22(NMP22) at a cut-off point of 5.27 ng/ml were 78.3% and 32.4%, respectively, which was lower than the findings in a study by Zippe et al with a sensitivity and specificity of 100% and 85% respectively at a cut-off point of 10.0 units per ml.²³ The difference between the findings of the two studies may be because the latter study was in a population of subjects with bladder cancers with predominantly TCC histology, against this study with predominantly squamous cell variety that arose on a background of chronic urinary schistosomiasis. Kumar et al in a study involving about 400 patients using the NMP22 quantitative test at a cut-reference value of 6-20U/ml, demonstrated that NMP22 had an overall sensitivity of 70-80%; however, it involved evaluation of subjects with recurrent TCC²⁴ as against the predominantly SCC in our environment.²⁴

A study by Salama et al from India showed that urine NMP22 levels increased significantly in the malignant group as against benign or healthy controls corroborating the reports of other authors; however, false-positive tests in the evaluation of NMP22 were alluded to, being due to the presence of urinary tract infection, inflammation or malignancy associated with other organs of genitourinary origin.²⁵ A negative result of the urine NMP22 test in 21.7% of the 46 patients with biopsy-confirmed bladder

cancer compared to 49% of 130 patients from a study by Salama et al from India.²⁵ In this study, the sensitivity and specificity of urine NMP22 were 78.3% and 32.4% of the 46 patients with biopsy-confirmed bladder cancer compared to 84.4% and 59.3% of 65 patients with biopsy-confirmed bladder cancer from a study by Salama et al.²⁵ Interestingly, their study did not show any significant increase in NMP22 levels among patients with bilharzial compared to non-bilharzial bladder cancers. The authors attributed lower urine NMP22 levels to patients in the squamous cell carcinoma group. A study by Akaza et al from Japan showed that urinary NMP22 levels might be affected by the size of the tumour.²⁶ The sensitivity of urine NMP22 in this study may be explained by the differences in the threshold, the components of the control group (benign and normal conditions) and lastly, to the absolute level of the marker as regards a correction factor with the level of creatinine in the urine.²⁵ The false-positive rates of urine NMP22 increased with the age of patients, as such there is a need to include an age-related reference when carrying out the study.²⁷ Urine NMP22 quantitative test in this study at a cut-off of 5.27ng/ml had a PPV and NPV of 59.0% and 54.6%, respectively, which was within the range of values for sensitivity (47-100%) from previous studies by Volpe et al.²⁸ However, the specificity (60-80%) from that same study was much higher when compared to this study. Another survey by Casetta et al using urine NMP22 quantitative test in bladder cancer diagnosis revealed a PPV and NPV of 81.6% and 29.9%, respectively, at a cut-off point of 11 U/ml amongst patients with high suspicion for bladder cancers and those with recurrent bladder cancers.²⁹ Though these values differ from the index study, it can be explained by the type of bladder cancers in such studies, which were mainly transitional cell carcinomas. The population are a mixture of suspicious and those with recurrent bladder cancers. The mean concentration of urine NMP22 in the study group was 6.27±1.40 ng/ml compared to the control group, 5.89±1.22 ng/ml, with no significant difference (p=0.197). The results of this study are at variance with other researchers, who reported significantly higher levels in bladder cancer than controls.^{30,31} Still, their studies comprised only patients with transitional cell carcinoma of the bladder. A similar study by Lekili et al found urinary NMP22 levels in bladder cancer patients to be significantly higher than the control group attributing it to the elevation and release of nuclear mitotic apparatus

protein from tumour cells in detectable levels, with a 25-fold more significant than normal cells due to cell death.^{31,32} The differences observed between this study's urine NMP22 quantitative test and urine cytology were statistically significant ($p < 0.001$) which may be accounted for by the smaller sample size of our study compared with the previous studies. Using the ROC curve, the NMP22 quantitative test was more effective than urine cytology in the present study. The sensitivity and specificity of urine cytology in the present study were 58.7% and 100.0%, respectively. Abdel-El-Gawad et al and Kristen et al reported sensitivities of 54.3%, 20.0-53.0% respectively while specificities of 100.0%, 83.0-99.0% respectively.^{31,7} The pattern of urine cytology results and their accuracy depends on several factors related to the tumour grade, method of sampling, nature of the specimen, and the skill of the pathologist.^{33,34} There is the need for quick processing of specimens, refrigerating or immediate fixation of the specimen with 50% ethanol for several days whenever there is a delay to yield increased sensitivity.³⁵

The reason mentioned above may explain the low sensitivity of urine cytology in this study. The diagnostic yield of urine cytology for low-grade urothelial cancers is lower, with a sensitivity and specificity as low as 8.5 and 50%, respectively. The nature of the urine specimen seems to impart the predictive value of the urine cytology, with voided samples being more specific and slightly less sensitive than instrumental urine sampling.³⁶ Voided cytology has been widely accepted as an adjunct to cystoscopy because of its noninvasiveness. The high specificity of cytology is counteracted by its low sensitivity, ambiguous test results, expense, and time lag to obtain reports

This study's high degree of urine cytology specificity (100%) could result from the absence of reactive changes associated with instrumental urine sampling. The resultant cell clustering further makes interpreting the cytologic specimens from this study straightforward.³⁷ Studies have corroborated the findings that with an increasing number of samples, there is a proportional increase in the sensitivity of urine cytology, especially regarding detecting high-grade lesions.³⁴ The diagnostic accuracy of urine cytology was high in this study though lower than found in a similar survey by El-Bolkainy et al from Egypt, which showed a higher value regarding squamous cell carcinomas (95%).³⁸ Bladder cancers of squamous cell origin associated with Bilharziasis are often well-differentiated and recognized quickly on cytology.³⁹ There is also higher exfoliation of cells from squamous cell carcinomas than other variants like adenocarcinoma and anaplastic.³⁸ Using the ROC curve, urine NMP22 performed better than urine cytology with a higher AUC of 0.538 than the AUC of cytology of 0.207 though the difference was not statistically significant ($p = 0.552$). The lower specificity of the urine NMP22 quantitative test in this study may not be unrelated because the commonest predisposition to the

development of bladder carcinoma in this study was chronic schistosomiasis, an inflammatory process causing false-positive results in the absence of bladder carcinoma. In this study, *Schistosoma* ova was detected in the biopsy specimens of 47.8% of the patients with bladder carcinoma; this is comparable to 50% and 46% reported in our environment and Tanzania with endemicity *Schistosoma*.⁴ The finding of *Schistosoma* ova in the biopsy specimens of some bladder carcinoma patients in this study was not particular to SCC. Some patients with TCC also had similar results. This corroborates the picture in the literature, confirming that schistosomiasis can predispose to other histopathological types of bladder carcinoma in pure or mixed forms.² In the current study, squamous cell carcinoma (85%) was more common than transitional cell carcinoma (15%). The results corroborate an earlier study by Abdulwahab-Ahmed et al which reported that the most common variety of diagnosed bladder cancers in Sokoto is the squamous cell carcinoma type due to the high prevalence of urinary schistosomiasis unlike transitional cell carcinoma variant found worldwide.³⁷ Finding from this current study was far higher than a similar survey done in our environment, which may be due to the increased awareness and availability of endoscopic equipment in our centre with the attendant workforce to cater for their evaluation.^{4,40} The occurrence of squamous cell carcinoma in our study reflects the difference in a risk factor in bladder cancer in our study environment and as similarly reported in Tanzania.⁴¹ Seventy-four per cent of the patients alluded to a history of untreated urinary schistosomiasis many years before symptoms. This confirms the preponderance of SCC among the subjects in this study, as previously reported in the literature.⁴ A significant proportion of the patients (47.8%) had histological confirmation of schistosomiasis on histology, confirming SCC occurrence in this population.

Limitations

Limitations of current study were; the sample size was relatively small due to the duration of the study and no investigations carried out to determine the clinical stage of the disease to correlate with the urinary marker to access aggressiveness and prognosticate in terms of TCC or SCC.

CONCLUSION

Urinary NMP22 quantitative assay has a low specificity for diagnosing bladder cancer, however, urine cytology is superior to urine NMP22 quantitative test. Therefore, the clinical value of urine NMP22 in the diagnosis of bladder cancer in our environment is questionable. Further multicentre studies involving large number of subjects from within schistosoma endemic areas as well as from non-endemic regions are needed to evaluate the clinical utility of NMP22 in the diagnosis of bladder cancer.

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