Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/rkme0e28

NMP-22 AND URINARY CYTOLOGY AS DIAGNOSTIC TOOLS IN CARCINOMA BLADDER: A PROSPECTIVE ANALYSIS

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ABSTRACT

Background: Bladder cancer is a common urological malignancy with high recurrence rates requiring lifelong surveillance. While cystoscopy remains the gold standard, it is invasive and costly. Voided urine cytology offers high specificity but poor sensitivity, especially in low-grade tumors. Nuclear Matrix Protein 22 (NMP-22) has emerged as a promising noninvasive urinary biomarker for bladder cancer detection and monitoring.

Methods: A prospective study was conducted at Command Hospital, Kolkata, from January 2009 to June 2010, involving 67 patients (23 fresh cases, 44 on follow-up). All patients underwent voided urine cytology, NMP-22 Bladder Chek testing, and cystoscopy, with histopathology serving as the reference standard. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for both tests.

Results: Of 67 patients, 41 had bladder carcinoma confirmed by histopathology. NMP-22 demonstrated a sensitivity of 68.29%, specificity of 88.46%, PPV of 90.32%, and NPV of 63.88%. In contrast, voided urine cytology showed a sensitivity of 12.19%, specificity of 100%, PPV of 100%, and NPV of 41.93%. Grade-wise analysis revealed NMP-22 sensitivity of 75% for low-grade and 69.56% for high-grade tumors, whereas cytology detected only 12.5% and 13.04%, respectively. Both tests failed to detect PUNLMP.

Conclusion: NMP-22 is significantly more sensitive than urine cytology, particularly for low-grade tumors, and offers a reliable adjunct to cystoscopy in bladder cancer detection and surveillance. While cytology remains highly specific, its limited sensitivity restricts its standalone use. Larger multicentric studies are warranted to validate NMP-22 as a standard surveillance tool.

Keywords: Bladder cancer, NMP-22, urine cytology, cystoscopy, urinary biomarkers, transitional cell carcinoma

INTRODUCTION

Bladder cancer is one of the most prevalent urological malignancies, ranking as the fourth most common cancer in men and ninth in women (1). Its global incidence is rising, with a 55% increase in yearly occurrence among men in the past 26 years (2). The incidence varies geographically, with higher rates in North America (23.8 per lakh) compared to lower rates in Melanesian men (2.7 per lakh), and in Indian men, it ranges from 2.6 to 4.8 per lakh in urban areas (3,4). In the United States alone, about 56,000 new cases are reported annually, with approximately 500,000 cases prevalent

overall (5,6). More than 95% of bladder cancers are transitional cell carcinomas (TCC) (7,8), with 70% being superficial, 25% muscle-invasive, and 5% carcinoma in situ. Notably, 50–70% of superficial tumours recur within two years after resection, necessitating regular cystoscopy-based follow-up (9,10).

Although cystoscopy remains the gold standard for bladder cancer diagnosis, it has limitations, including false-negative results ranging from 10–40% and difficulty detecting carcinoma in situ (11,12). Additionally, cystoscopy is invasive, uncomfortable, and costly (13). Even with technological advancements like fluorescence cystoscopy using intravesical 5-aminolevulinic acid, false negatives persist, with one multicenter study reporting 37% of biopsies from suspicious cystoscopic findings being negative (14, 15). To complement cystoscopy, voided urine cytology is widely used. However, its sensitivity is variable (11–76%) (16,17), with particularly low detection rates for low-grade tumours (20–60%) compared to over 80% for high-grade tumours (18-21). While urine cytology offers high specificity, it is observer-dependent, time-consuming, and requires multiple samples (22-25). Moreover, its accuracy varies across institutions (26), and after BCG therapy, results may be inconclusive (27, 28). Low adherence to frequent surveillance protocols further limits its utility (29). These challenges highlight the need for a more sensitive, noninvasive, and reliable diagnostic tool for bladder cancer detection and monitoring. An ideal test would serve both as an adjunct to cystoscopy and a possible replacement for urine cytology. Such a marker should be noninvasive, rapid, easy to interpret, and cost-effective while maintaining high sensitivity and specificity. While population-wide screening may not be cost-effective due to relatively low prevalence (30,31), targeted screening of high-risk groups—such as smokers and those exposed to carcinogens—could help in early detection. Moreover, in patients with a history of bladder cancer, an effective urinary biomarker could aid in early recognition of recurrence and potentially reduce dependence on invasive cystoscopy.

NMP-22 (Nuclear Matrix Protein 22) has emerged as a promising urinary tumour marker. This 236-kilodalton protein plays a structural and regulatory role in the nucleus and is released into urine when urothelial cells undergo apoptosis or necrosis (32-35). In bladder cancer patients, urinary NMP-22 levels can rise up to 25-fold (36-38). However, benign urinary conditions such as infections, stones, haematuria, and instrumentation may cause false positives (39). Initially developed as a quantitative assay, NMP-22 has evolved into a qualitative, immunochromographic point-of-care test that provides results within 20–50 minutes. Approved by the US FDA, it is inexpensive, rapid, noninvasive, and independent of pathologist interpretation (40). Although its sensitivity and specificity are not yet ideal, NMP-22 represents a significant advancement in urinary-based tumour markers and has the potential to complement or replace urine cytology in clinical practice (23,25). Given the scarcity of indigenous data, the present study was undertaken to evaluate its diagnostic value.

MATERIAL AND METHODS

The present prospective study was conducted at Command Hospital, Kolkata, from January 2009 to June 2010, involving 67 patients comprising both freshly detected cases of carcinoma bladder and those on follow-up. All eligible patients (excluding those with benign inflammatory or infectious conditions, calculi, foreign bodies, bowel interposition, other genitourinary cancers, recent instrumentation, or bleeding disorders) underwent voided urine cytology, performed three times, and NMP-22 testing immediately prior to cystoscopy. Cystoscopy, with histopathological confirmation where applicable, was used as the reference standard. Clinical and investigative data, including Hb, USG KUB, urine cytology, NMP-22, cystoscopy findings, and histopathology, were recorded systematically. The diagnostic accuracy of NMP-22 and urine cytology was assessed by calculating sensitivity, specificity, positive predictive value, and negative predictive value. The NMP-22 test was performed using freshly voided urine, with results interpreted as positive, negative, or inconclusive based on standard kit instructions.

OBSERVATIONS AND RESULTS

TABLE 1: DEMOGRAPHIC PROFILE

Total number of cases	67
Male: Female	57:10
Age (Range)	(20-87) years
Mean age	55.9 years
Median age	62 years
Fresh cases	23
Follow up cases	44

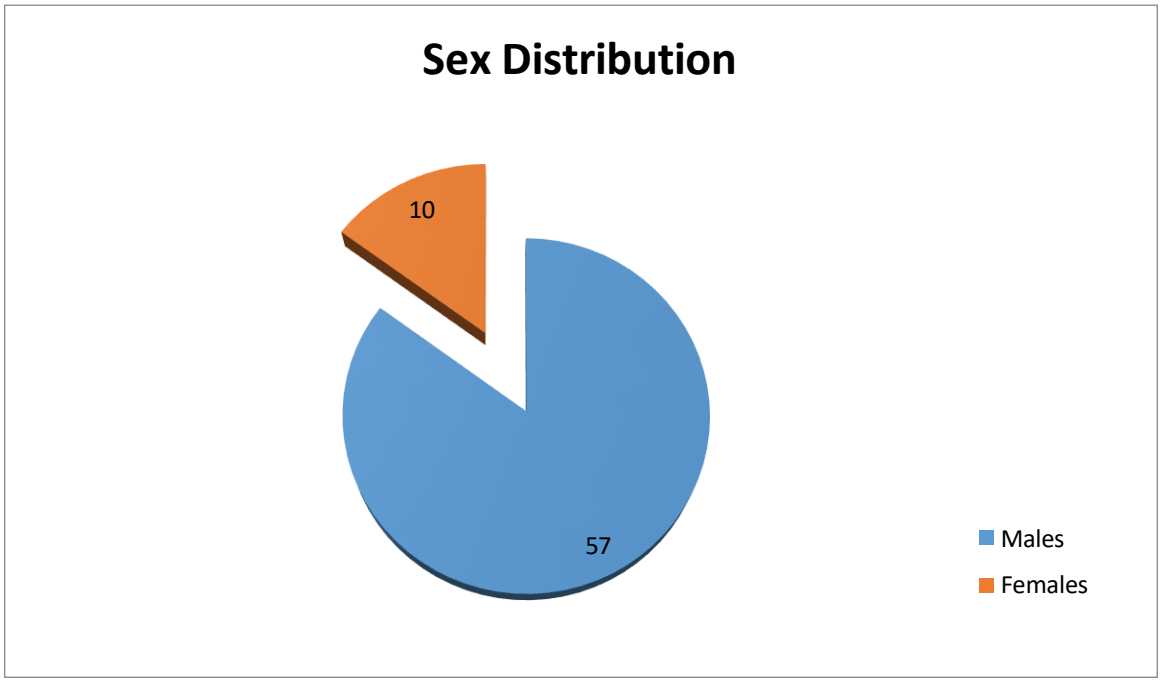

Figure (1)

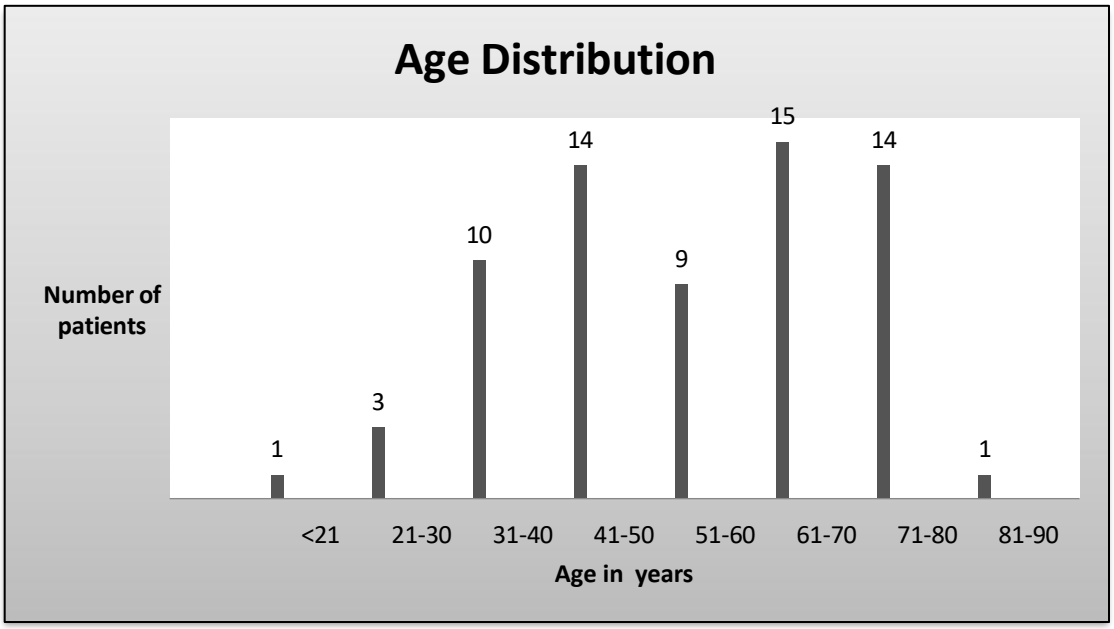

Figure (2)

Histopathological Grading

Out of the 67 patients enrolled in the study, 26 patients were found to have no growth on cystoscopy. The remaining 41 patients underwent TURBT followed by histopathological examination of the resected tissue.

TABLE 2: HISTOPATHOLOGICAL GRADING

Histopathological Grading	Number of Patients
Grade 1	01
Grade 2	16
Grade 3	23
No malignancy	01

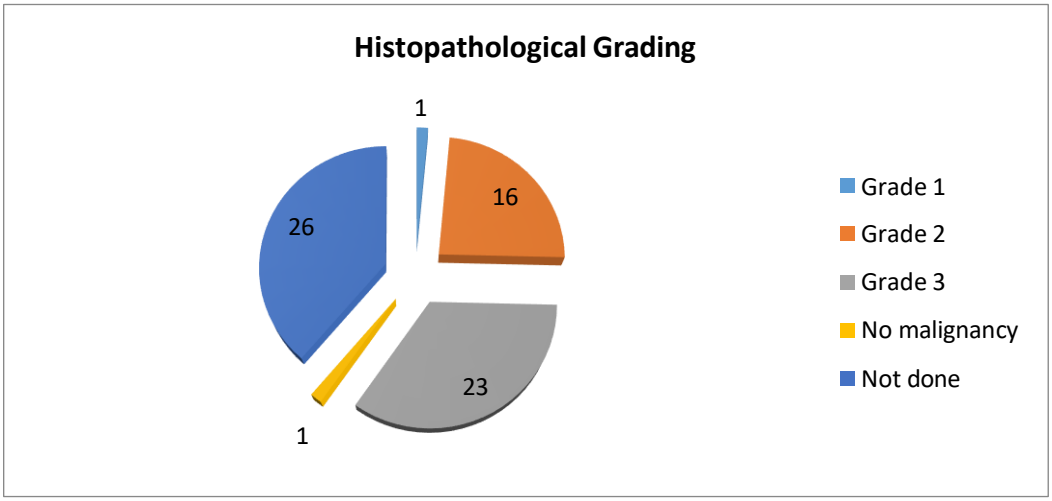

Figure (3)

NMP-22 Bladder Chek Test

The NMP-22 test was done in all the 67 cases. It was positive in 31 cases and negative in 36 cases. Carcinoma bladder was present in 40 cases. The NMP-22 bladder Chek test was positive in 28 cases of carcinoma bladder and negative in 12 cases of carcinoma bladder.

TABLE 3: COMPARISON OF NMP-22 BLADDER CHEK TEST WITH CYSTOSCOPY

n = 67	Cystoscopy Positive	Cystoscopy Negative	Total
NMP-22 Positive	28	03	31
NMP-22 Negative	13	23	36
Total	41	26	67

Sensitivity of NMP-22
= True Positive/True Positive + False Negative= 28/28+13 = 28/41 = 68.29%
Specificity of NMP-22
= True Negative/True Negative + False Positive = 23/23+3 = 23/26 = 88.46%
Positive Predictive value
= True positive/ True Positive + False Positive = 28/28+3 = 28/31 = 90.32%
Negative Predictive value
= True Negative/ True Negative + False Negative = 23/23+13 =23/36 = 63.88%

Voided urine cytology

Voided urine cytology was done in all 67 cases.
It was negative in 62 cases.
It was positive in 4 cases and suspicious/atypical in 01 case.
Out of the 62 cases which were negative on cytology, 35 were subsequently found to have bladder cancer on histopathological examination, 01 was found to have no malignancy while 26 were not subjected to HPE as cystoscopy did not reveal any lesion. These 26 cases and the 01 declared negative for malignancy on HPE (ie total 27 cases) were interpreted as bladder carcinoma absent cases.
All 4 cases found positive on cytology were confirmed to have bladder cancer on histopathological examination. The 01 case declared suspicious on cytology has been interpreted as VUC positive in the table below and was also found to have bladder cancer on histopathological examination.

TABLE 4: COMPARATIVE STUDY OF THE VOIDED URINE CYTOLOGY WITH CYSTOSCOPY

	Cystoscopy Positive	**Cystoscopy Negative**	**Total**
Voided urine cytology Positive	05	00	05
Voided urine cytology Negative	36	26	62
Total	41	26	67

Sensitivity of voided urine cytology
= True Positive/True Positive + False Negative = 05/05+36 = 05/4 = 12.19%
Specificity of voided urine cytology
= True Negative/True Negative + False Positive = 26/26+0 = 26/26 = 100%
Positive Predictive value
= True positive/True Positive + False Positive = 05/05+0 = 05/05 = 100%
Negative Predictive value
= True Negative/True Negative + False Negative = 26/26+36 =26/62 = 41.93%
All five cases which were detected to be positive by voided urine cytology were detected positive by cystoscopy as well.

Comparison of NMP-22 versus voided urine cytology

Out of 41cases found positive on cystoscopy, NMP-22 was positive in 28 cases where as cytology was positive in 05 (including the 01 case which was reported as suspicious/atypical) cases. The sensitivity was therefore 68.29% and 12.19% respectively (Table 5 and 6).
Out of 26 patients in whom cystoscopy was negative, NMP-22 was negative in 23 cases, giving a specificity of 88.46% where as voided urine cytology was negative in all the 26 cases, thus giving a specificity of 100% (Table 5 and 6). All the 05 cases which were detected as positive by voided urine cytology were detected to be positive by NMP-22 as well.

TABLE 5: COMPARISON OF NMP-22 VERSUS VOIDED URINE CYTOLOGY

n=67	**NMP-22 Positive**	**NMP-22 Negative**	**Total**
Voided urine cytology Positive	05	00	05
Voided urine cytology Negative	26	36	62
Total	31	36	67

TABLE 6: COMPARISON OF NMP-22 VERSUS VOIDED URINE CYTOLOGY

	NMP-22	**Voided urine cytology**
Sensitivity (%)	68.29	12.19
Specificity (%)	88.46	100
Positive predictive value (%)	90.32	100
Negative predictive value (%)	63.88	41.43

Comparison of NMP-22 and voided urine cytology as per HPE grades.

Out of 67 patients, biopsy was done in 41 cases as the rest of the cases had no visible growth on cystoscopy. The biopsies were reported variously as No malignancy, Papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade urothelial carcinoma and high grade urothelial carcinoma.

The 01 case of PUNLMP could not be detected as positive by either NMP-22 or voided urine cytology.

In case of low grade cancers (n=16) ie G_2, NMP-22 was positive in 12 cases where as voided urine cytology was positive in only 02 cases (Out of these two cases, 01 was reported as suspicious/atypical).

In case of High grade cancers ie G_3 (n=23), NMP-22 was positive in 16 cases where as voided urine cytology was positive in 03 cases only.

The one case reported as negative on histopathological examination was reported as negative by NMP-22 and voided urine cytology as well.

Among 16 patients with low grade cancers, NMP-22 was positive in 75% (n= 12) of cases as compared to voided urine cytology which was positive in 12.5% (n=02). In case of high grade cancers ie G3 (n=23), NMP-22 was positive in 69.56% (n= 16) cases where as voided urine cytology was positive in 13.04% (n= 03) cases only.

TABLE 7: GRADE WISE COMPARISON OF NMP-22 VERSUS VOIDED URINE CYTOLOGY

Total no. of patients in whom biopsy done (n=41)	**NMP-22**		**Voided urine cytology**	
	Positive	**Negative**	**Positive**	**Negative**
No Malignancy (n=01)	(n=0) 0%	(n=1) 100%	(n=0) 0%	(n=01) 100%
PUNLMP (n=01)	(n=0) 0%	(n=1) 100%	(n=0) 0%	(n=01) 100%
Low Grade (n=16)	(n=12) 75%	(n=04) 25%	(n=02) 12.5%	(n=14) 87.5%
High Grade (n=23)	(n=16) 69.56%	(n=07) 30.04%	(n=03) 13.04%	(n=20) 86.96%

TABLE 8: GRADE WISE COMPARISON OF SENSITIVITY AND SPECIFICITY OF NMP-22 AND VOIDED URINE CYTOLOGY

Grade	Sensitivity	
	NMP-22	Voided urine cytology
Grade I (PUNLMP)	0%	0%
Grade II (Low grade)	75%	12.5%
Grade III (High grade)	69.56%	13.04%

DISCUSSION

Bladder cancer is one of the most prevalent malignancies, ranking fourth in men and ninth in women, with a significant rise in recurrence rates over the past 15 years (1,2). Transitional cell carcinoma accounts for more than 95% of cases, with cystoscopy remaining the gold standard for diagnosis and follow-up (8,11). However, cystoscopy is invasive, uncomfortable, and prone to false positives (up to 40%), while carcinoma in situ may also escape detection (12,13). Voided urine cytology has been used as an adjunctive tool, but its limitations—such as variable sensitivity ranging from 7% to 65%, observer dependency, and inconclusive results post-BCG therapy—reduce its reliability, particularly in low-grade tumor (16,17). Moreover, compliance with prolonged cystoscopic surveillance remains low, with only 40% adherence to guidelines (29).

In this context, NMP-22 has emerged as a promising adjunct to cystoscopy. It is a simple, rapid, and less observer-dependent test that detects tumor-related proteins in urine samples (40). Several studies have reported variable sensitivity and specificity values, with Talwar et al noting that NMP-22 (52.4%) could replace urine cytology (9.5%) in follow-up of low-grade tumors (41). The present study demonstrated a sensitivity of 68.29% and specificity of 88.46% for NMP-22, results comparable or superior to earlier reports such as Witjes et al (75%, 81.6%) and Talwar et al (67.3%, 80.5%) (41,42). The positive predictive value (PPV) of NMP-22 in this study (90.32%) was markedly higher than those reported by Ponsky et al (34.1%), Witjes et al (56.3%), and Zippe et al (29%) (39,42,43). However, its negative predictive value (NPV) of 63.88% was lower than some earlier studies, including Witjes et al (91.2%) and Zippe et al (100%) (42,43). In contrast, voided urine cytology in this study showed very poor sensitivity (12.19%) compared to other studies, but its specificity (100%) and PPV (100%) remained high, aligning with Del Nero et al and Talwar et al (41, 44) .

Grade-wise analysis revealed that NMP-22 had better sensitivity for low-grade (75%) compared to high-grade tumors (69.56%), while both NMP-22 and cytology failed to detect PUNLMP. Voided urine cytology, although highly specific, showed poor sensitivity across both low-grade (12.5%) and high-grade (13.04%) tumors. These findings reaffirm existing literature that urinary cytology is particularly weak in detecting low-grade tumors but more reliable for high-grade lesions (18-21).

Overall, the study highlights the superior diagnostic utility of NMP-22 compared to urine cytology in bladder cancer surveillance. While cytology remains highly specific, its poor sensitivity limits its role as a standalone test. NMP-22, with higher sensitivity and strong PPV, appears to be a more effective adjunct to cystoscopy, particularly in low-grade tumor detection. However, given variability in reported results, larger studies and standardized protocols are needed to fully establish its role in routine clinical practice.

CONCLUSION

The present study demonstrates that the NMP-22 BladderChek test provides superior diagnostic performance compared to voided urine cytology in patients with bladder cancer. With higher sensitivity and positive predictive value, NMP-22 is particularly effective in detecting low-grade tumors, where cytology is least reliable. Although cytology remains highly specific, its limited sensitivity restricts its role as an independent diagnostic tool. NMP-22, being noninvasive, rapid, and cost-effective, can serve as a valuable adjunct to cystoscopy in both diagnosis and follow-up of bladder cancer patients. However, variability in results across studies highlights the need for larger multicenter trials and standardization of protocols before its widespread adoption in routine clinical practice.

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