Int J Clin Exp Med 2016;9(5):7965-7975
www.ijcem.com /ISSN:1940-5901/IJCEM0018722

Original Article

Nuclear matrix protein 22 (NMP22) test in the diagnosis of bladder cancer: a meta-analysis

Lei Fu[1,2*], Rong Wang[3*], Ling Yin[1], Pengjun Zhang[4], Yaping Tian[1], Maochang Niu[1]

[1]Core Laboratory of Translational Medicine, Chinese PLA General Hospital, Beijing 100853, China; [2]Department of Medical Engineering, 401 Hospital of Chinese PLA, Qingdao 266071, China; [3]National Research Institute for Family Planning, Beijing 100081, China; [4]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education of China), Department of Interventional Therapy, Peking University Cancer Hospital and Institute, Beijing, 100142, China. [*]Equal contributors.

Received October 28, 2015; Accepted March 17, 2016; Epub May 15, 2016; Published May 30, 2016

Abstract: We aimed to assess the diagnostic value of the nuclear matrix protein 22 (NMP22) test in detecting bladder cancer. We searched public databases including PubMed, Springer, MEDLINE, Elsevier Science Direct, Google scholar and Cochrane Library published before September 2015. Cystoscopy and voided urine cytology (VUC) were golden standards. Sensitivity, specificity, positive likelihood ratio (LR), negative LR and diagnostic odds ratio (DOR) of NMP22 test from included studies were meta-analyzed. The summary receiver operating characteristic (SROC) curve was constructed, and the area under the curve (AUC) and an index Q* were summarized. Subgroup analyses were performed. In addition, Egger's test was used to detect publication bias. A total of 24 studies consisting of 8848 patients with bladder cancer were included in the present meta-analysis. The results of sensitivity, specificity, positive LR, negative LR and DOR of NMP22 test were 0.71 (95% CI = 0.69 to 0.72), 0.80 (95% CI = 0.79 to 0.81), 2.99 (95% CI = 2.42 to 3.71), 0.42 (95% CI = 0.35 to 0.50) and 7.45 (95% CI = 5.32 to 10.43) respectively. The AUC and Q* index were 0.7846 and 0.7225, respectively. Subgroup analysis suggested that cutoff value might be one source of heterogeneity. Egger's test showed that no publication bias existed ($P > 0.05$). The NMP22 test may be appropriate for detecting bladder cancer, but it cannot replace the cystoscopy and VUC in the clinical diagnosis. Further studies are needed to unify the cut-off value and evaluate the diagnostic efficiency of NMP22 test.

Keywords: Nuclear matrix protein 22, bladder cancer, diagnosis, meta-analysis

Introduction

Bladder cancer is one of the most common cancers occurring worldwide [1], represents an important cause of morbidity and mortality [2]. Early diagnosis of bladder cancer remains a challenge [3]. Cystoscopy is the standard method for detection of bladder cancer. However, it is an invasive, costly and uncomfortable procedure which results in bacteriuria within 48 hours [4]. A non-invasive urinary marker test can improve the diagnosis accuracy of bladder cancer by increasing the accuracy of detection.

Nuclear matrix protein 22 (NMP22) associates with the mitotic apparatus and has been reported as a non-invasive urinary biomarker in detecting bladder cancer [2]. However, the diagnostic value of the NMP22 test for detecting bladder cancer is still controversial. Sensitivity and specificity of the NMP22 test ranged from 33% to 100% and from 40% to 93%, respectively [5]. Several studies showed that the NMP22 test was an effective and sensitive screening test for detecting bladder tumors, and it could be used as a substitute for voided urine cytology (VUC) [6, 7]. In addition, cystoscopy is also a tool that used for detection of bladder cancer. Some studies showed that the NMP22 test could not replace cystoscopy (a gold standard for detecting bladder cancer), but it could increase the accuracy of cystoscopy [8-10]. However, some other studies stated that the NMP22 test could not be adopted as a routine tool for screening or surveillance of the

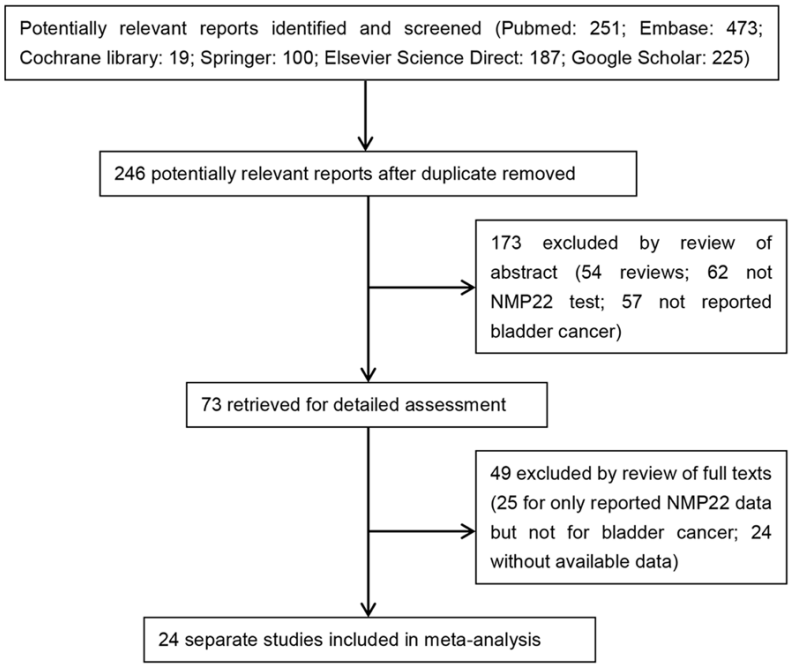

Figure 1. The screening and selection process of the included studies.

patients with superficial bladder cancer due to its poor specificity or sensitivity [11, 12].

In order to synthetically evaluate the diagnostic value of the NMP22 test for patients with bladder cancer, we systematically reviewed the published findings and quantitatively combined the results using meta-analysis.

Material and methods

Source of material

We retrieved several public databases, mainly including PubMed, Springer, MEDLINE, Elsevier Science Direct, Google scholar and Cochrane Library published up to September 2015. The keywords of "Nuclear matrix protein 22" or "NMP22", or "diagnosis" and "bladder cancer" or "bladder carcinoma" or "bladder tumor" and "study" or "trial" were used for searching. In addition, references from retrieved studies were checked to collect additional relevant studies. Publication date and publication language were not restricted in our research.

Search methods

There were four investigators (author A, B, C and D) independently retrieved the electronic databases. An independent retrieve for PubMed, Springer and MEDLINE was performed by A and B with the same method. An independent retrieve for Elsevier Science Direct, Google scholar and Cochrane Library was performed by C and D with the same method. The disagreements were resolved by discussion.

Inclusion and exclusion criteria of studies

The studies met the following criteria were included: (1) the investigations of the patients with bladder cancer and the diagnosis of bladder cancer using NMP22 test; (2) cystoscopy or VUC are conventionally considered as the gold standard for the diagnosis of bladder cancer; (3) the NMP22 test for diagnosis of bladder cancer was provided in papers; (4) the effect sizes were sensitivity, specificity, positive likelihood ratio (LR), negative LR and DOR. Sample size, gender or ranges of age were not limited. We only collected data from the full-published papers, and didn't extract any data from meeting or conference abstracts. We excluded the reviews, reports and the reduplicated studies.

Data extraction and study quality assessment

We extracted data items including study details (e.g. the first author's name, publication year of study, location of participants, etc.) and characteristics of subjects (e.g. age, gender and sample size, etc.). Two investigators (A and D) extracted data independently using the standard protocol, and the third investigator reviewed their results. We contacted authors of included studies to obtain further information that needed clarification. Discrepancies were resolved by discussing with our research team or contracting with original investigators. We recorded the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) of the NMP22 test.

Table 1. Characteristics of the included study

Author, year	Country	Sample size	Male (%)	Age, y (mean or Min-Max)	Gold standard	NMP22 detection method	Study design	Cutoff value	NMP22 test			
									TP	FP	FN	TN
Wiener 1998	Austria	291	68	17-90	Cystoscopy	NMP22 test kit	CS	10 U/mL	44	62	47	138
Ramakumar 1999	USA	196	78	29-102	Cystoscopy	NMP22 test kit	CC	10 U/mL	30	56	27	83
Sharma 1999	USA	278	NA	NA	Office cystoscopy and bladder biopsy	NMP22 test kit	CS	10 U/mL	28	44	6	200
Giannopoulos 2000	Greece	168	86	66	Cystoscopy	NMP22 assay kit	CS	10 U/mL	51	37	18	62
Mian 2000	Italy	240	NA	22-92	Cystoscopic and histologic evaluations	The NMP22 test (Matritech)	CS	10 U/mL	30	39	24	147
Casella 2000	Switzerland	235	70	23-97	Cystoscopy	NMP22 test kit	CS	10 U/mL	66	18	64	87
Poulakis 2001	Germany	739	66	37-90	Cystoscopy and biopsy	NMP22 test kit	CS	10 U/mL	321	85	101	232
Gutierrez 2001	Spain	150	NA	20-91	Cystoscopy	NMP22 test kit	CS	10 U/mL	58	7	18	67
Saad 2002	UK	120	83	30-88	Histology	NMP22 test kit	CS	10 U/mL	42	9	10	59
Toma 2004	Germany	120	NA	NA	Cystoscopy	The NMP22 test (Matritech)	CS	10 U/mL	29	27	13	51
Kumar 2006	India	131	89	32-91	Cystoscopy	NMP22 Bladder Chek test kit	CS	10 U/mL	39	19	7	66
Sun 2006	China	251	71	33-84	Cystoscopy	NMP22 detection kits	CC	10 U/mL	117	19	34	81
Hutterer 2008	Canada	2687	75	6-97	Cystoscopy	NMP22 test kit	CS	10 U/mL	906	284	263	1234
Gupta 2009	India	145	87	25-83	Cystoscopy	NMP-22 Bladder Chek test kit	CS	10 U/mL	48	20	8	69
Tritschler 2007	Germany	100	71	67.9	Histologic examination	NMP-22 Bladder Chek test kit	CS	10 U/mL	26	36	14	24
Kehinde 2011	Kuwait	150	NA	16-77	Cystoscopy, bladder biopsy	NMP22 qualitative assay kits	CS	6 U/mL	51	26	22	51
Kelly JD 2012	UK	1396	62	60.7	Pathological confirmation	FDA-approved NMP22H Test Kit	CS	10 U/mL	104	192	91	1009
Stampfer 1997	USA	231	72	68	Cystoscopy	NMP22 test kit	CS	10 U/mL	32	17	34	191
Sankhwar 2013	India	646	44	18-91	Cystoscopy with biopsy	NMP22 test kit	CS	10 U/mL	44	55	35	512
Landman 1998	USA	77	87	72.3	Pathologic evaluation	NMP22 test kit	CC	7 U/mL	38	7	9	23
Serretta 1998	Italy	137	89	65	Cystoscopy	NMP22 test kit	CC	10 U/mL	30	58	12	37
Soloway 1996	USA	112	NA	NA	Cystoscopy	A home NMP22 urine collection kit	CS	10 U/mL	23	17	10	62
Li 2013	China	175	142	62.4 (23-89)	Final histologic results	NMP22 Bladder Chek test kit	CS	NA	48	5	23	37
Yafi 2015	Canada	109	90	69 (33-96)	Cystoscopy with biopsies	Commercially available kits	CS	NA	48	4	35	22

Notes: TP, true positive; FP, false positive; FN, false negative; TN, true negative.

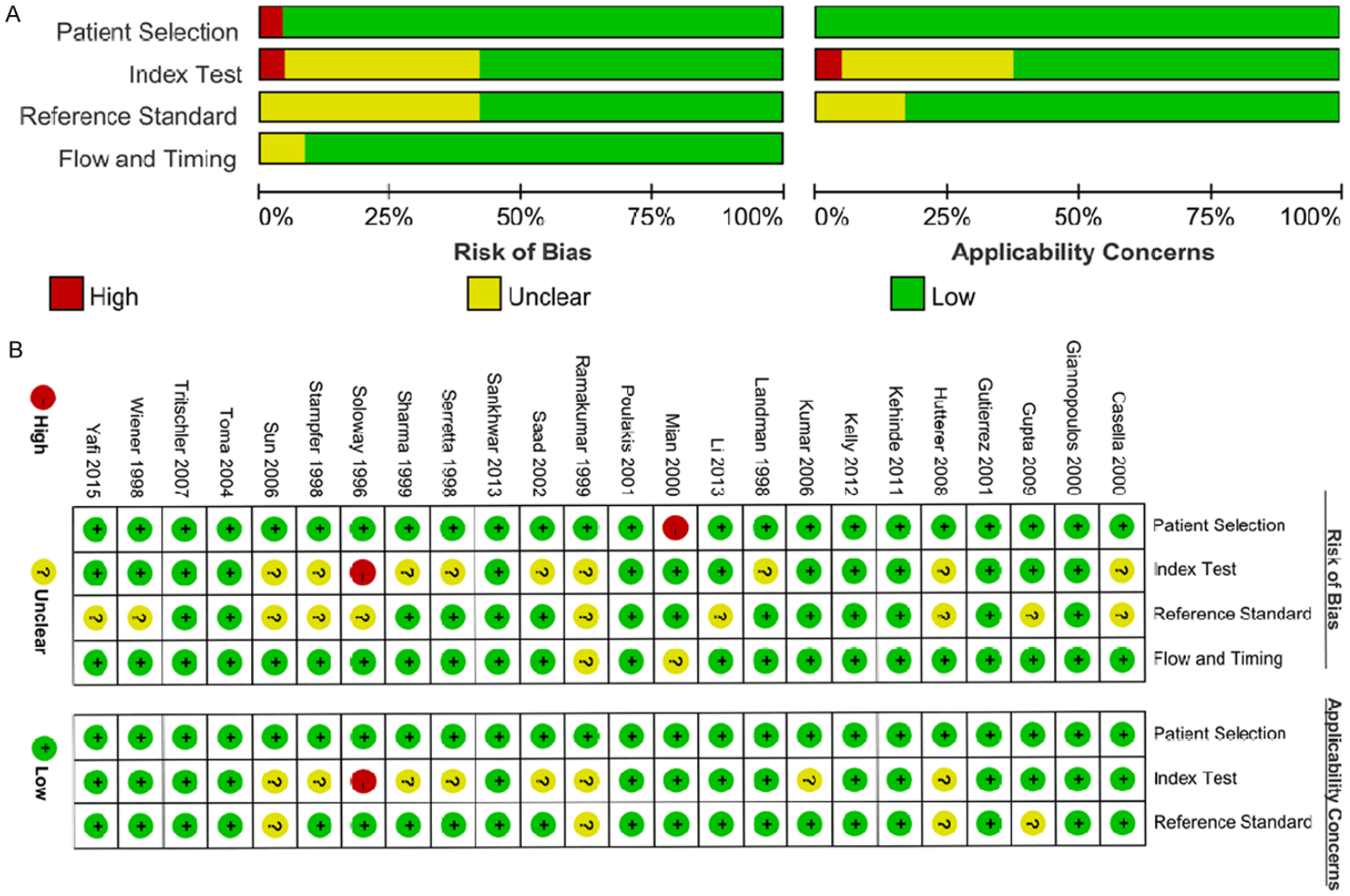

Figure 2. A. Methodological quality graph; B. Methodological quality summary.

Table 2. Meta-analysis results of the NMP22 test in diagnosis of bladder cancer

Parameter	Test of association		Test of heterogeneity			Model
	Estimates	95% *CI*	*Q*	*P* value	I^2 (%)	
Sensitivity	0.71	0.69 to 0.72	170.21	< 0.01	86.5	-
Specificity	0.80	0.79 to 0.81	300.72	< 0.01	92.4	-
Positive LR	2.99	2.42 to 3.71	250.97	< 0.01	90.8	Random
Negative LR	0.42	0.35 to 0.50	199.28	< 0.01	88.5	Random
DOR	7.45	5.32 to 10.43	178.28	< 0.01	87.1	Random

Notes: LR, Likelihood Ratio; DOR, Diagnostic Odds Ratio.

The Quality Assessment of Diagnosis Accuracy Studies (QUADAS-2) [13] was used for the quality assessment of all the contained studies.

Statistical analyses

All statistical analyses were performed by using the Meta-DiSc software v.1.4 (http://www.hrc.es/investigacion/metadisc_en.htm) and the STATA software package v.11.0 (Stata Corporation, College Station, TX, USA). The heterogeneity was assessed by using Cochran's *Q*-statistic [14] and I^2 test [15]. The effect sizes were combined by using random effects model. The estimates of the sensitivity, specificity, positive LR, negative LR, DOR and the corresponding 95% confidence interval (95% CI) for each study were pooled. The summary receiver operating characteristic (SROC) curve was constructed to describe diagnostic accuracy over a range of threshold values. The area under the curve (AUC) and Q* index were summarized. In addition, Egger's test [16] was performed to detect the publication bias in this study. All the *P*-values were two-sided, and the $P \leq 0.05$ was considered statistically significant.

Besides, subgroup analysis was performed according to gold standard (Cystoscopy, Pathological or Histology), study design (cohort study, case-control study) and cutoff value (10, others) to explore the influence of these factors on the results.

Results

Characteristics of eligible studies

The study selection process was shown in **Figure 1**. A total of 1255 potentially relevant studies were retrieved by the search terms (PubMed: 251; Springer: 100; Embase: 473; Elsevier Science Direct: 187; Google Scholar: 225; Cochrane Library: 19). There were 246 potentially relevant studies after removing duplicates or irrelevant papers by reading the title. Then, 173 articles were excluded by screening abstract (54 were review articles; 62 not included NMP22 test; 57 not reported bladder cancer). Further, 49 studies which did not accord with the inclusion criteria were excluded (25 for only reported NMP22 data but not for bladder cancer; 24 not available data).

Finally, the remained 24 studies [6-12, 17-33] were included in the present meta-analysis. The characteristics of these studies were shown in **Table 1**. The included studies were published between 1998 and 2015. A total of 8848 patients with bladder cancer were included in this meta-analysis.

The results of quality assessment were shown in risk of bias and applicability concern. The QUADAS-2 indicated that all 24 studies had higher quality, and patient selection, index test, reference standard and flow and timing had lower risk of bias (**Figure 2**).

Meta-analysis

The overall meta-analysis of bladder cancer patients with the NMP22 test was summarized in **Table 2**. We used the random effects model (heterogeneity: $I^2 > 50\%$, $P < 0.01$) to combine the estimates. The pooled sensitivity (0.71, 95% CI = 0.69 to 0.72), specificity (0.80, 95% CI = 0.79 to 0.81), positive LR (2.99, 95% CI = 2.42 to 3.71), negative LR (0.42, 95% CI = 0.35 to 0.50) and DOR (7.45, 95% CI = 5.32 to 10.43) of NMP22 test were shown in **Figure 3**. It showed that the AUC and Q* index were 0.7846 and 0.7225, respectively (**Figure 4**). No threshold effects (Spearman correlation coefficient = 0.077, P = 0.719 > 0.05) were found from the SROC curve.

Subgroup analysis results of the NMP22 test in diagnosis of bladder cancer were shown in **Table 3**. The subgroup results based on gold standard and study design had no significant

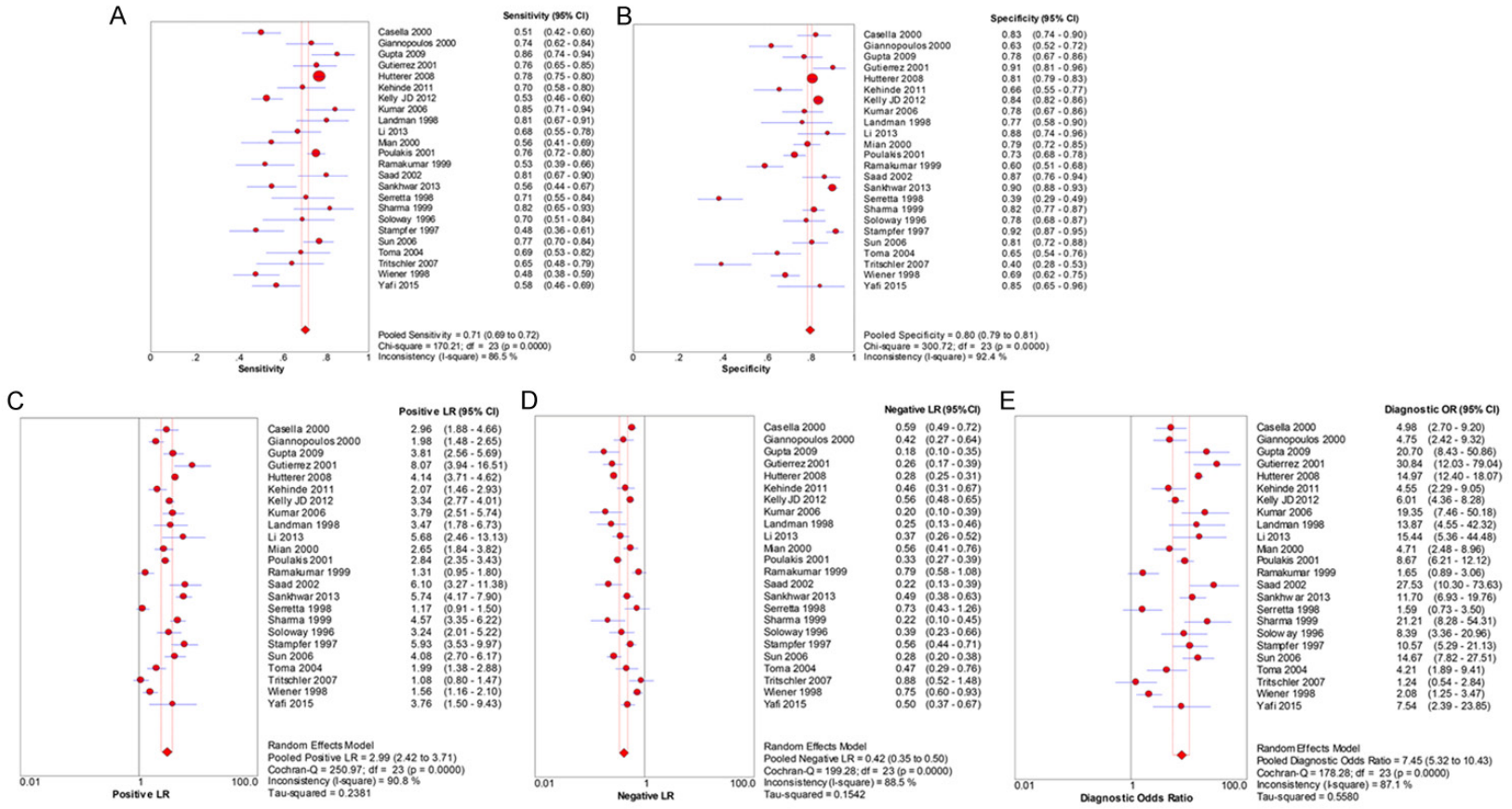

Figure 3. The pooled sensitivity (A), specificity (B), positive LR (C), negative LR (D) and DOR (E) of NMP22 test in detection bladder cancer.

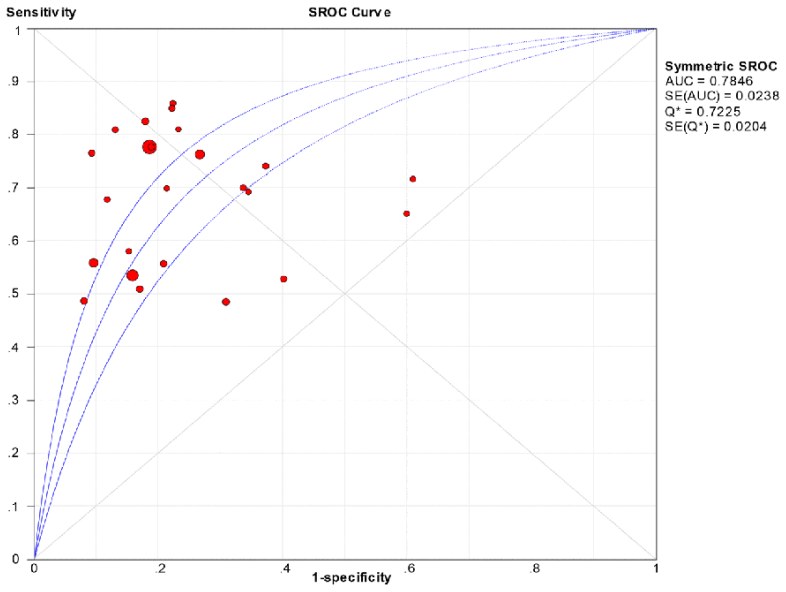

Figure 4. The summary receiver operating characteristic (SROC) curve. AUC represent the area under the SROC curve.

difference with the overall meta-analysis results. However, significant difference was found in others cutoff (except cutoff = 10) between subgroup analysis results and overall meta-analysis results (P > 0.01).

No evidence of publication bias was found from the Egger's test for this meta-analysis (*t* = -1.79, *P* = 0.087).

Discussion

Many studies [6, 8, 11] have reported the diagnostic value of the NMP22 test in detecting bladder cancer, but these studies have shown mixed results. In this meta-analysis, we combined 24 separate studies consisting of 8848 patients to evaluate the diagnostic value of the NMP22 test in detecting bladder cancer. The results showed that NMP22 test might be appropriate for detecting bladder cancer.

NMP22 is a nuclear protein that is associated with chromatid regulation and cell separation during replication [34]. NMP22 is released from the nuclei of tumor cells after they die, and it can be detected in urine. Some studies found that urinary levels of NMP22 in patients with bladder cancer might be greater than levels in healthy subjects [7, 35]. The NMP22 test has been used from many clinical studies to screen the potential bladder cancer. In this meta-analysis, NMP22 test showed relatively high sensitivity and specificity. However, in a recent meta-analysis, NMP22 test showed a higher sensitivity than VUC (0.43, 95% CI = 0.40 to 0.46) and a lower specificity than VUC (0.97, 95% CI = 0.96 to 0.98) and the pooled positive LR (10.56, 95% CI = 6.21 to 17.96), negative LR (0.62, 95% CI = 0.54 to 0.72) and DOR (18.24, 95% CI = 10.54 to 31.57) of NMP22 test were all lower than VUC [36]. Thus, we conclude that NMP22 test cannot be an independent tool for detecting bladder cancer. Kumar et al. suggest that NMP22 test cannot replace cystoscopy and can be used as an adjunct to the cystoscopy which is a gold standard for detecting bladder cancer [7].

In this meta-analysis, sensitivity and specificity of each study varied in a wide range. It may be due to the methodological defects of original studies such as cut-off value. A simple variation of the cut-off value may result in quite different values of sensitivity and specificity without any actual change in the underlying test's accuracy [37]. In our included studies, the NMP22 was detected with cut-off value vary from 6-10 U/ml. Meanwhile, sensitivity in one included study was 84.21% for NMP22 at the cutoff value of 6 U/ml and 76.32% with 10 U/ml [18]. Therefore, a uniform cut-off value of the NMP22 test is important for stability and credibility of the sensitivity.

Despite some studies have meta-analyzed the diagnostic value of NMP22 test on bladder cancer, some significant advances in our study should be considered. Our meta-analysis included more (24 studies) and newer [8] studies than previous studies [38-40]. Furthermore, these results are in accord with our meta-analysis. Moreover, no publication bias was observed in this study.

Some limitations of this study should be also discussed. Heterogeneity is a common limita-

Table 3. Subgroup analysis results of the NMP22 test in diagnosis of bladder cancer

Parameter	Test of association		Test of heterogeneity			Model
	Estimates	95% *CI*	*Q*	*P* value	I^2 (%)	
All studies						
Gold standard						
Cystoscopy (n = 19)						
Sensitivity	0.72	0.70 to 0.74	135.87	< 0.01	86.8	-
Specificity	0.79	0.78 to 0.80	235.90	< 0.01	92.4	-
Positive LR	2.96	2.34 to 3.75	197.28	< 0.01	90.9	Random
Negative LR	0.42	0.35 to 0.52	169.29	< 0.01	89.4	Random
DOR	7.35	5.03 to 10.73	144.57	< 0.01	87.5	Random
Pathological or Histology (n = 5)						
Sensitivity	0.64	0.59 to 0.68	23.13	< 0.01	82.7	-
Specificity	0.82	0.80 to 0.84	58.42	< 0.01	93.2	-
Positive LR	3.22	1.65 to 6.29	51.87	< 0.01	92.3	Random
Negative LR	0.41	0.27 to 0.62	21.98	< 0.01	81.8	Random
DOR	8.08	3.18 to 20.53	28.16	< 0.01	85.8	Random
Study design						
Cohort study (n = 21)						
Sensitivity	0.71	0.69 to 0.73	159.28	< 0.01	87.4	-
Specificity	0.81	0.80 to 0.82	189.89	< 0.01	89.5	-
Positive LR	3.24	2.66 to 3.94	158.32	< 0.01	87.4	Random
Negative LR	0.41	0.34 to 0.49	174.54	< 0.01	88.5	Random
DOR	8.39	6.07 to 11.59	130.82	< 0.01	84.7	Random
Case-control (n = 3)						
Sensitivity	0.67	0.59 to 0.75	9.90	< 0.01	79.8	-
Specificity	0.54	0.48 to 0.60	17.12	< 0.01	88.3	-
Positive LR	1.58	0.97 to 2.58	10.37	< 0.01	80.7	Random
Negative LR	0.55	0.28 to 1.05	11.08	< 0.01	82.0	Random
DOR	3.05	0.96 to 9.69	11.94	< 0.01	83.2	Random
Cutoff value						
10 U/mL (n = 20)						
Sensitivity	0.71	0.70 to 0.73	160.82	< 0.01	88.2	-
Specificity	0.80	0.79 to 0.81	290.26	< 0.01	93.5	-
Positive LR	2.95	2.34 to 3.73	243.33	< 0.01	92.2	Random
Negative LR	0.42	0.35 to 0.52	194.30	< 0.01	90.2	Random
DOR	7.24	4.99 to 10.52	173.07	< 0.01	89.0	Random
Others (n = 4)						
Sensitivity	0.68	0.62 to 0.73	7.77	0.05	61.4	-
Specificity	0.76	0.69 to 0.82	8.82	0.03	66.0	-
Positive LR	3.21	1.94 to 5.33	7.21	0.07	58.4	Random
Negative LR	0.40	0.33 to 0.49	4.87	0.18	38.4	Fixed
DOR	7.80	5.03 to 12.09	4.99	0.17	39.9	Fixed

Notes: LR, Likelihood Ratio; DOR, Diagnostic Odds Ratio.

tion of the meta-analysis [41], and threshold effect is one of the main sources of heterogeneity in diagnostic meta-analysis. In this study, we did not find threshold effects from the SROC curve. However, the heterogeneities were highly significant. Thus, we performed subgroup analysis according to gold standard (Cystoscopy, Pathological or Histology), study design (cohort

study, case-control study) and cutoff value (10, others) to explore the influence of these factors on the results. The subgroup analysis results had no significant difference with overall meta-analysis results and heterogeneities remained highly significant. It suggested that gold standard and study design were not the source of heterogeneities. Significant difference was found in others cutoff (except cutoff = 10) between subgroup analysis results and overall meta-analysis results, and thus cutoff value may be one source of heterogeneity. Furthermore, distinct NMP22 test kits, enzyme-labeled instruments and ethnicities among the studies also may be the source of heterogeneity. In addition, we didn't evaluate the tumor grade, stage, and recurrence. In one contained study, the sensitivity increased with the rising of tumor grade and stage and was higher in recurrence group than in non-recurrence group [25]. These factors may affect the diagnosis accuracy of the NMP22 test.

In conclusion, our study shows that the NMP22 test may be appropriate for detecting bladder cancer, but it cannot replace the cystoscopy and VUC in the clinical diagnosis. Further studies are needed to unify the cut-off value and evaluate the diagnostic efficiency of the NMP22 test in detection of the bladder cancer.

Acknowledgements

This work was supported by National Natural Science Foundation of China (Key Program) under Grant No. 71532002. We would like to thank all participants in this study and all of people who give the help for this study.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ling Yin, Core Laboratory of Translational Medicine, Chinese PLA General Hospital, No. 28, Fuxing Road, Haidian District, Beijing 100853, China. Tel: +86-010-66937547; Fax: +86-010-66937547; E-mail: yylldr@163.com

References

[1] Sartini D, Muzzonigro G, Milanese G, Pozzi V, Vici A, Morganti S, Rossi V, Mazzucchelli R, Montironi R and Emanuelli M. Upregulation of tissue and urinary nicotinamide N-methyltransferase in bladder cancer: Potential for the development of a urine-based diagnostic test. Cell Biochem Biophys 2013; 65: 473-483.

[2] Shariat SF, Savage C, Chromecki TF, Sun M, Scherr DS, Lee RK, Lughezzani G, Remzi M, Marberger MJ, Karakiewicz PI and Vickers AJ. Assessing the clinical benefit of nuclear matrix protein 22 in the surveillance of patients with nonmuscle-invasive bladder cancer and negative cytology. Cancer 2011; 117: 2892-2897.

[3] Srivastava AK, Singh PK, Srivastava K, Singh D, Dalela D, Rath SK, Goel MM, Lal M and Bhatt B. Diagnostic role of survivin in urinary bladder cancer. Asian Pac J Cancer Prev 2013; 14: 81-85.

[4] Almallah Y, Rennie C, Stone J and Lancashire M. Urinary tract infection and patient satisfaction after flexible cystoscopy and urodynamic evaluation. Urology 2000; 56: 37-39.

[5] Mowatt G, Zhu S, Kilonzo M, Boachie C, Fraser C, Griffiths T, N'Dow J, Nabi G, Cook J and Vale L. Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. Health Technol Assess 2010; 14: 1-331, iii-iv.

[6] Stampfer DS, Carpinito GA, Rodriquez-Villanueva J, Willsey LW, Dinney CP, Grossman HB, Fritsche HA and McDougal WS. Evaluation of NMP22 in the detection of transitional cell carcinoma of the bladder. J Urol 1998; 159: 394-398.

[7] Kumar A, Kumar R and Gupta NP. Comparison of NMP22 BladderChek test and urine cytology for the detection of recurrent bladder cancer. Jpn J Clin Oncol 2006; 36: 172-175.

[8] Sankhwar M, Singh R, Sankhwar SN, Goel MM, Jain A and Sankhwar PL. Nuclear Matrix Protein 22 in Voided Urine Cytology Efficacy in Risk Stratification for Carcinoma of Bladder. World J Oncol 2013; 4: 151-157.

[9] Casella R, Huber P, Blöchlinger A, Stoffel F, Dalquen P, Gasser TC and Lehmann K. Urinary level of nuclear matrix protein 22 in the diagnosis of blaader cancer: experience with 130 patients with biopsy confirmed tumor. J Urol 2000; 164: 1926-1928.

[10] Mian C, Lodde M, Haitel A, Vigl EE, Marberger M and Pycha A. Comparison of the monoclonal UBC-ELISA test and the NMP22 ELISA test for the detection of urothelial cell carcinoma of the bladder. Urology 2000; 55: 223-226.

[11] Serretta V, Lo Presti D, Vasile P, Gange E, Esposito E and Menozzi I. Urinary NMP22 for the detection of recurrence after transurethral resection of transitional cell carcinoma of the bladder: experience on 137 patients. Urology 1998; 52: 793-796.

[12] Tritschler S, Scharf S, Karl A, Tilki D, Knuechel R, Hartmann A, Stief CG and Zaak D. Validation of the Diagnostic Value of NMP22® BladderChek® Test as a Marker for Bladder Cancer by Photodynamic Diagnosis. Eur Urol 2007; 51: 403-408.

[13] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA and Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529-536.

[14] Deeks JJ, Altman DG and Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. Systematic Reviews in Health Care: Meta-Analysis in Context, Second Edition 2001; 285-312.

[15] Higgins J, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[16] Egger M, Smith GD, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[17] Poulakis V, Witzsch U, De Vries R, Altmannsberger H, Manyak M and Becht E. A comparison of urinary nuclear matrix protein-22 and bladder tumour antigen tests with voided urinary cytology in detecting and following bladder cancer: the prognostic value of false-positive results. BJU Int 2001; 88: 692-701.

[18] Gutierrez Banos J, Rebollo Rodrigo M, Antolin Juarez F and Martin Garcia B. NMP22, BTA stat test and cytology in the diagnosis of bladder cancer: a comparative study. Urol Int 2001; 66: 185-190.

[19] Wiener H, Mian C, Haitel, Haitel A, Pycha A, Schatzl G and Marberger M. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? J Urol 1998; 159: 1876-1880.

[20] Ramakumar S, Bhuiyan J, Besse JA, Roberts SG, Wollan PC, Blute ML, O'Kane DJ. Comparison of screening methods in the detection of bladder cancer. J Urol 1999; 161: 388-394.

[21] Sharma S, Zippe CD, Pandrangi L, Nelson D and Agarwal A. Exclusion criteria enhance the specificity and positive predictive value of NMP22* and BTA stat. J Urol 1999; 162: 53-57.

[22] Giannopoulos A, Manousakas T, Mitropoulos D, Botsoli-Stergiou E, Constantinides C, Giannopoulou M and Choremi-Papadopoulou H. Comparative evaluation of the BTAstat test, NMP22, and voided urine cytology in the detection of primary and recurrent bladder tumors. Urology 2000; 55: 871-875.

[23] Saad A, Hanbury D, McNicholas T, Boustead G, Morgan S and Woodman A. A study comparing various noninvasive methods of detecting bladder cancer in urine. BJU Int 2002; 89: 369-373.

[24] Toma MI, Friedrich MG, Hautmann SH, Jäkel KT, Erbersdobler A, Hellstern A and Huland H. Comparison of the ImmunoCyt test and urinary cytology with other urine tests in the detection and surveillance of bladder cancer. World J Urol 2004; 22: 145-149.

[25] Hutterer GC, Karakiewicz PI, Zippe C, Lüdecke G, Boman H, Sanchez-Carbayo M, Casella R, Mian C, Friedrich MG and Eissa S. Urinary cytology and nuclear matrix protein 22 in the detection of bladder cancer recurrence other than transitional cell carcinoma. BJU Int 2008; 101: 561-565.

[26] Kehinde EO, Al-Mulla F, Kapila K and Anim JT. Comparison of the sensitivity and specificity of urine cytology, urinary nuclear matrix protein-22 and multitarget fluorescence in situ hybridization assay in the detection of bladder cancer. Scand J Urol Nephrol 2011; 45: 113-121.

[27] Gupta NP, Sharma N and Kumar R. Nuclear matrix protein 22 as adjunct to urine cytology and cystoscopy in follow-up of superficial TCC of urinary bladder. Urology 2009; 73: 592-596.

[28] Sun Y, He DL, Ma Q, Wan XY, Zhu GD, Li L, Luo Y, He H and Yang L. Comparison of seven screening methods in the diagnosis of bladder cancer. Chin Med J (Engl) 2006; 119: 1763.

[29] Kelly JD, Dudderidge TJ, Wollenschlaeger A, Okoturo O, Burling K, Tulloch F, Halsall I, Prevost T, Prevost AT and Vasconcelos JC. Bladder cancer diagnosis and identification of clinically significant disease by combined urinary detection of Mcm5 and nuclear matrix protein 22. PLoS One 2012; 7: e40305.

[30] Landman J, Chang Y, Kavaler E, Droller MJ, Liu BC. Sensitivity and specificity of NMP-22, telomerase, and BTA in the detection of human bladder cancer. Urology 1998; 52: 398-402.

[31] Soloway MS, Briggman JV, Carpinito GA, Chodak GW, Church PA, Lamm DL, Lange P, Messing E, Pasciak RM and Reservitz GB. Use of a new tumor marker, urinary NMP22, in the detection of occult or rapidly recurring transitional cell carcinoma of the urinary tract following surgical treatment. J Urol 1996; 156: 363-367.

[32] Li HX, Wang MR, Zhao H, Cao J, Li CL and Pan QJ. Comparison of fluorescence in situ hybridization, NMP22 bladderchek, and urinary liquid-based cytology in the detection of bladder urothelial carcinoma. Diagn Cytopathol 2013; 41: 852-857.

[33] Yafi FA, Brimo F, Steinberg J, Aprikian AG, Tanguay S and Kassouf W. Prospective analysis of

sensitivity and specificity of urinary cytology and other urinary biomarkers for bladder cancer. Urol Oncol 2015; 33: 66 e25-31.
[34] Stefanopoulos A and Economopoulos KP. Screening for urinary bladder cancer with the use of nuclear matrix protein (NMP) 22: is it feasible? Tob Induc Dis 2014; 12: A6.
[35] Keesee SK, Briggman JV, Thill G and Wu YJ. Utilization of nuclear matrix proteins for cancer diagnosis. Crit Rev Eukaryot Gene Expr 1996; 6: 189-214.
[36] Guo A, Wang X, Shi J, Sun C and Wan Z. Bladder tumour antigen (BTA stat) test compared to the urine cytology in the diagnosis of bladder cancer: A meta-analysis. Can Urol Assoc J 2014; 8: e347-352.
[37] Charoensawat S, Böhning W, Böhning D and Holling H. Meta-analysis and meta-modelling for diagnostic problems. BMC Med Res Methodol 2014; 14: 56.
[38] Lotan Y and Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. Urology 2003; 61: 109-118.
[39] Glas AS, Roos D, Deutekom M, Zwinderman AH, Bossuyt PM, Kurth KH. Tumor markers in the diagnosis of primary bladder cancer. A systematic review. J Urol 2003; 169: 1975-1982.
[40] van Rhijn BW, Van der Poel HG and van Der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. European Urol 2005; 47: 736-748.
[41] Moreno SG, Sutton AJ, Thompson JR, Ades A, Abrams KR and Cooper NJ. A generalized weighting regression-derived meta-analysis estimator robust to small-study effects and heterogeneity. Stat Med 2012; 31: 1407-1417.