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TIMELY REVIEW

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Diagnostic performance of nuclear matrix protein 22 and urine cytology for bladder cancer: A meta-analysis

Jie Wang BM[1] | Xi Zhao BM[2] | Xiao Lei Jiang BM[1] | Dong Lu MS[1] | Qiang Yuan MS[1] | Jiabing Li PhD[3]

[1]The Second Affiliated Hospital of North Sichuan Medical College, Sichuan Mianyang 404 Hospital, Mianyang, China

[2]Dalian Medical University, Dalian Medical University Graduate School, Dalian, China

[3]Mianyang Maternal and Child Health Hospital, Sichuan Mianyang 404 Hospital, Mianyang, China

Correspondence
Jiabing Li, Mianyang Maternal and Child Health Hospital, Sichuan Mianyang 404 Hospital, Mianyang 621000, China.
Email: wj22021412@163.com

Abstract

Purpose: To compare and analyze the diagnostic efficacy of nuclear matrix protein 22 (NMP22) and urine cytology (UC) in the diagnosis of bladder cancer.

Methods: Search the Chinese and English studies on NMP22 and urinary cytology in the diagnosis of bladder tumors published between 1999 and June, and conduct quality evaluation, data extraction and analysis.

Results: A total of 397 related articles were retrieved, and 12 articles were finally included after screening, including 2456 subjects. The heterogeneity test shows that there is no discernible threshold effect. Perform meta-analysis according to the random effects model. The results showed that the total sensitivity of NMP22 and UC were 0.79 (95% CI [0.73, 0.84]) (CI: Confidence interval), 0.55 (95% CI [0.41, 0.69]), and the total specificity 0.59 (95% CI [0.46], respectively, 0.71), 0.91 (95% CI (0.81, 0.96]), +LR 1.9 (95% CI [1.4, 2.6]) (+LR: positive likelihood ration), 5.9 (95% CI [3.3, 10.6]), −LR 0.35 (−LR: negative likelihood ration), respectively (95% CI [0.27, 0.47]), 0.49 (95% CI [0.38, 0.64]), diagnostic odds ratios 5 (95% CI [3, 9]), 12 (95% CI [7, 21]). The area under the summary receiver operating characteristics curve (AUC) was 0.79 (95% CI [0.75, 0.82]) and 0.81 (95% CI [0.77, 0.84]), respectively.

Conclusions: NMP22 has moderate diagnostic efficiency for bladder cancer. Its sensitivity is greater than UC, but its specificity is significantly lower than that of UC. At present, it cannot replace traditional cystoscopy and UC, but it can be combined to detect bladder tumors. It plays a major role in screening, postoperative monitoring and follow-up.

KEYWORDS

bladder tumor, diagnosis, meta analysis, nuclear matrix protein, urine cytology

Bladder cancer is part of the common malignant tumors of the genitourinary system in our country. It is under a very high incidence and fatality rate in our country, and its prevalence is rising all over the world, especially in developed countries.[1] According to data released in 2019,[2] the Morbidity of bladder cancer in my country in 2015 was 5.80 per 100,000, and the mortality rate was 2.37 per 100,000. Both of them ranked 13th in systemic malignancy. The incidence rate for male and female bladder cancer was 8.83/100,000 and 2.61/100,000; the mortality rate for men and women was 3.56/100,000 and 1.11/100,000 respectively. According to GLOBOCAN 2020 global cancer statistics,

Wang Jie and Zhao Xi contributed equally to this study.

there are approximately 573,000 new cases and 213,000 death. Males are more common than in women. The morbidity and mortality rates for men are 9.5 and 3.3 per 100,000, respectively, which is about four times that of women worldwide.[3] Early detection, diagnosis, and timely intervention are the keys to lower the risk of bladder tumor recurrence and progression. Many novel tumor markers have been discovered since the 1990s, and many have been approved by the FDA for early screening and postoperative monitoring of cystic cancer. Markers such as Fluorescence in situ hybridization (FISH), nuclear matrix protein 22 (NMP22), bladder tumor antigen (BTA stat, BTA TRAK), immune cells/UCYT+ and cytokeratin (CK-18, CK-20, and CYFRA21-1) can be used for urinary system tumors.[4] However, these tumor markers have their specific shortcomings.[5] For example, sensitivity and specificity of cystoscopy are good, but it is an invasive examination, which will bring certain pain to the patient, and may cause iatrogenic injury and infection. Urine cytology (UC) is non-invasive and highly specific, but it is greatly affected by factors such as the operator's experience, and its sensitivity is low. Especially for the screening of low grade tumors, it may be affected by urinary tract infections, kidney stone, and interference with bladder perfusion therapy.[6] Therefore, there is a need to search for a bladder tumor marker with high sensitivity and specificity to replace the current invasive cystoscopy and UC detection method with poor sensitivity.

Nuclear matrix protein (NMP) was first set out in 1974. It is a non-chromatin structure present in the nucleus of tumor cells. After cell death, NMP22 is released and is available in human urine in the form of soluble complexes or fragments. In liquid, its concentration in urothelial cancer cells is 25 times that of normal cells.[7] At the same time, urine NMP22 values of patients with bladder tumors have no correlation with serum NMP22 values. Urinary NMP22 is directly released by tumor cells, so the test results are more reliable. In recent years, there have been a lot of clinical studies on NMP22 in non-invasive bladder tumor screening and monitoring. NMP22 is considered to be an efficient substitute, either alone or in combination with UC. It is utilized to the diagnosis and screening of bladder tumors, grading and staging and predicting prognosis.[8] However, the results of some randomized, double-blind trials showed that the results of its diagnostic accuracy were inconsistent and fluctuating, causing clinicians to doubt the value of its diagnosis and screening. Based on this, this study conducted a systematic analysis of literature data on bladder cancer diagnosis by comparing relevant NMP22 and urinary cytology (UC) at home and abroad, and using cystoscopy or pathological examination as the gold standard to clarify its diagnostic value for bladder tumors, thus to provide a theoretical basis for the clinical diagnostics and treatment of bladder tumors.

1 | MATERIALS AND METHODS

1.1 | Inclusion and exclusion criteria

1.1.1 | Criteria for inclusion and exclusion of research subjects

1. The results of cystoscopy biopsy or postoperative pathological examination were used as the diagnostic gold standard, and the research subjects were patients diagnosed with or without bladder tumors by the gold standard;
2. UC check as a control group;
3. The study content provides the number of true positive, true negative, false positive, and false negative cases, or the complete data of the four-diagnosis table can be obtained by calculation.

Exclusion criteria:

1. The gold standard is not the above-mentioned histological evidence. The research subjects also have other urogenital tumors such as renal pelvis and ureter cancer, and independent bladder tumor data cannot be obtained;
2. Case report, review, conference abstract, non-clinical research literature, degree papers, and so forth;
3. The information provided is incomplete, and key data cannot be obtained.

1.1.2 | Measurement index

Sensitivity, specificity, +LR, −LR, diagnostic odds ratio (DOR), and summary receiver operating characteristics (SROC) area under curve (AUC).

1.2 | Search strategies

We systematically searched PubMed, Embase, Cochrane Library, the Web of Science, Wanfang, and CNKI from January 1999 to June 2021. Search terms included: "Urinary Bladder Neoplasms", "Bladder Neoplasms", "Bladder Tumors", "Urinary Bladder Cancer", "Malignant Tumor of Urinary Bladder", "Cancer of the Bladder", "Bladder Cancer", "Nuclear matrix protein 22", "NMP-22", "urine cytology", and the language is limited to Chinese and English.

1.3 | Research methodology

1.3.1 | Literature selection

Strictly select the literature depending on the inclusion and exclusion criteria. Two researchers independently screen the literature and remove the data. If there is a disagreement and it is difficult to assess whether to include it in the trial or not, the solution will be discussion or consultation with experts.

1.3.2 | Evaluation of literature quality

For the included studies, we use quality assessment of diagnostic accuracy studies-2 (QUADAS-2) in the Revman5.3 software.[9,10] To complete the evaluation of the two core aspects, the risk of bias and applicability, based on the description of the four key domains of case

selection: test to be evaluated, gold standard, case flow, and progress, and the answers to the questions in each domain. The risk of bias and applicability of each field of the original research were thus finally concluded "High", "Low" or "Unclear."

1.3.3 | Data extraction and statistical analysis

The main contents of the data extraction include: title, author, year of publication, sample size, age, diagnosis four-fold table, data of case group and control group, and heterogeneity test and meta analysis result through Stata14 and RevMan5.3. The heterogeneity test includes threshold and non-threshold effects, and the SROC curve is drawn to test whether there is heterogeneity caused by the threshold effect; the chi-square test and Q test are used for each effect size to detect whether there are other non-threshold effects that cause heterogeneity sex. If there is a non-threshold effect, select an appropriate model to merge according to the degree of heterogeneity. If $P > .100$ and $I^2 < 50\%$, use a fixed effects model for Meta analysis, otherwise use a random effects model for meta analysis. Calculate the combined sensitivity, specificity, +LR, −LR, DOR, draw a comprehensive receiver operating characteristic curve and calculate the curve under the curve area AUC. Simultaneously conduct meta regression and sensitivity analysis to identify the source of heterogeneity. In addition, draw a Deek funnel chart to analyze the publication bias of the study. If $P < .10$, it indicates that there is a certain publication bias. Draw a Fagan diagram to assess the clinical application value of NMP22 and UC, and $P < .05$ is examined statistically significant.

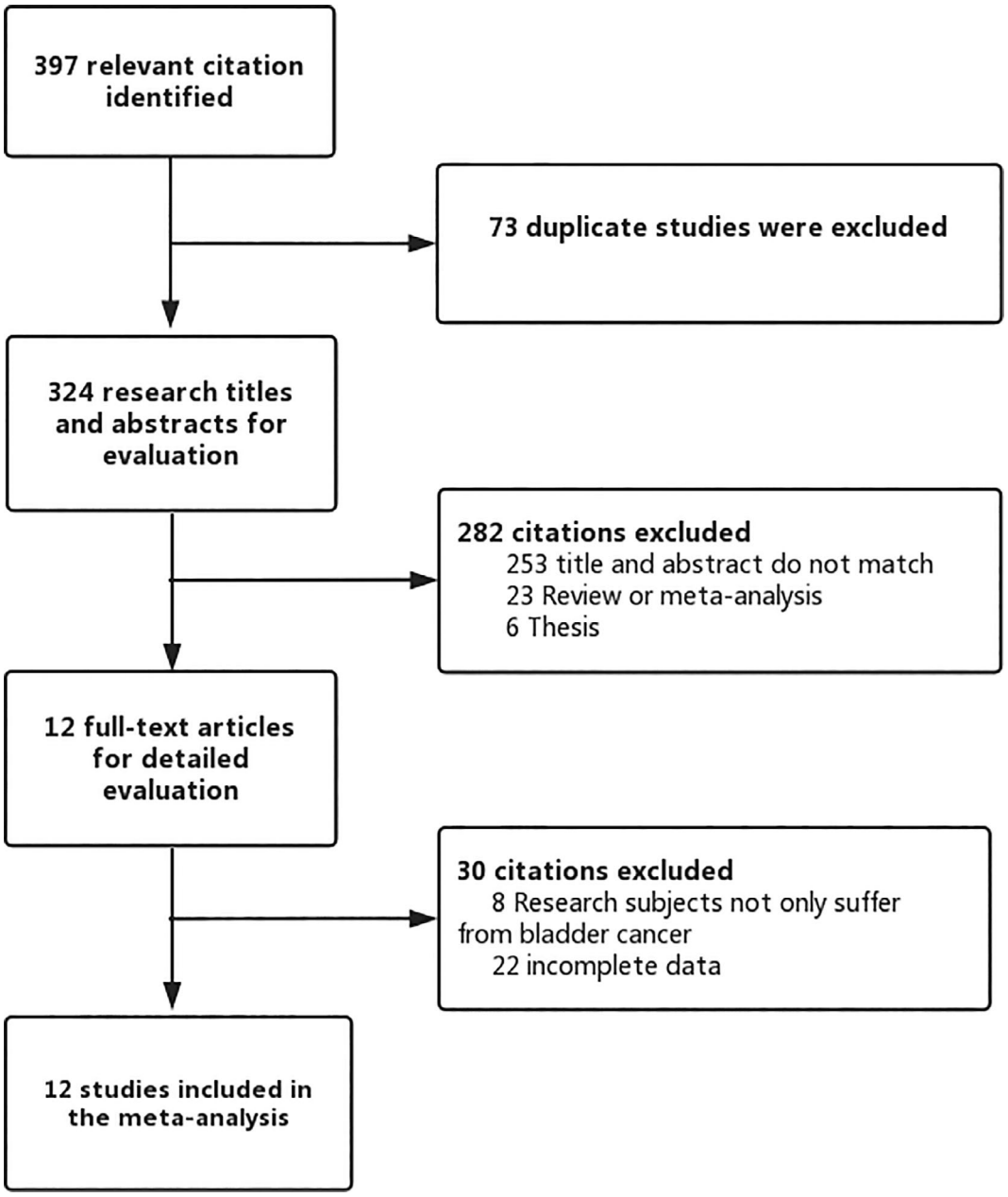

FIGURE 1 Flow chart of the inclusion and exclusion of the relevant studies

2 | RESULTS

2.1 | Literature search results

Results of the literature search 397 relevant literatures were retrieved, including 86 English literatures and 311 Chinese literatures. In strict accordance with the inclusion and exclusion criteria, 385 documents that did not meet the requirements such as duplicate documents, reviews, non-clinical research documents, and dissertations were removed, and 12 documents were finally included,[11–22] which included 2456 cases of study objects. All tests directly provide or can be calculated to obtain the complete data of the four-diagnosis table, and all evidence such as cystoscopy biopsy or postoperative pathological examination results is used as the gold standard. Refer to Figure 1 for details of the research content literature screening process. The basic characteristics of the included studies are presented in Table 1.

2.2 | Quality evaluation

The quality evaluation bar chart is depicted in Figure 2, and the risk bias entry and adaptability summary chart is shown in Figure 3.

2.3 | Bias analysis

1. Among the 12 included articles, most of them did not carry out or mention whether random sampling was carried out, and the possibility of selection bias was high;
2. Some experimental groups included patients with clear diagnosis, and the control group included some studies that did not use or mention whether blinding was used when judging the results of the experiment to be evaluated, which may cause bias;
3. NMP22 test and urine exfoliation cytology test The results need to be interpreted manually, and measurement bias may occur;
4. The urine collection method has been limited to the patient to urinate, so the possibility of confounding bias is small;
5. All patients only accepted the same gold standard, therefore the possibility of verification bias is small;
6. Although extensive search strategies are adopted, there are still some documents that are not available. Therefore, potential publication bias cannot be ruled out and should be considered when applying research results.

2.4 | Analysis of heterogeneity

2.4.1 | Threshold effect

In this article, the SROC curve is drawn to find out if there is heterogeneity caused by the threshold effect. When there is a threshold effect, sensitivity and specificity are adversely correlated (positively

TABLE 1 Basic characteristics of the included studies

References	Year	Age	Gender		Total	NMP22				UC				Gold standard
			Men	Women		TP	FP	FN	TN	TP	FP	FN	TN	
Sajid et al.,[23]	2020	40 ~ 66	300	80	380	176	134	31	39	116	155	10	99	Cystoscopy or pathological biopsy
Zhou et al.,[24]	2018	37 ~ 81	121	68	189	68	62	17	42	49	6	36	98	Cystoscopy or pathological biopsy
Yu et al.,[25]	2017	32 ~ 70	82	38	120	98	6	9	7	93	7	14	6	Cystoscopy or pathological biopsy
Li et al.,[26]	2016	32 ~ 79	36	14	50	13	20	2	15	6	2	9	33	Cystoscopy or pathological biopsy
Zhang et al.,[27]	2008	34 ~ 87	75	21	96	44	5	11	36	23	1	32	40	Cystoscopy or pathological biopsy
Kapila et al.,[28]	2008	30 ~ 78	38	8	46	18	13	5	10	7	3	16	20	Cystoscopy or pathological biopsy
You et al.,[29]	2003	30 ~ 87	118	37	155	62	18	33	42	41	10	54	50	Cystoscopy or pathological biopsy
Parekattil et al.,[30]	2003	16 ~ 89	182	71	253	19	123	8	103	18	43	9	183	Cystoscopy or pathological biopsy
Su et al.,[31]	2003	Average age, 64.8	53	39	92	22	19	2	49	9	2	15	66	Cystoscopy or pathological biopsy
Lahme et al.,[32]	2003	Not mentioned	Not mentioned		228	103	22	61	42	74	7	90	57	Cystoscopy or pathological biopsy
Poulakis et al.,[33]	2001	Average age, 66.7	485	254	739	321	101	85	232	252	13	154	320	Cystoscopy or pathological biopsy
Chen et al.,[18]	2019	33 ~ 84	72	36	108	49	5	19	35	17	0	51	40	Cystoscopy or pathological biopsy

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

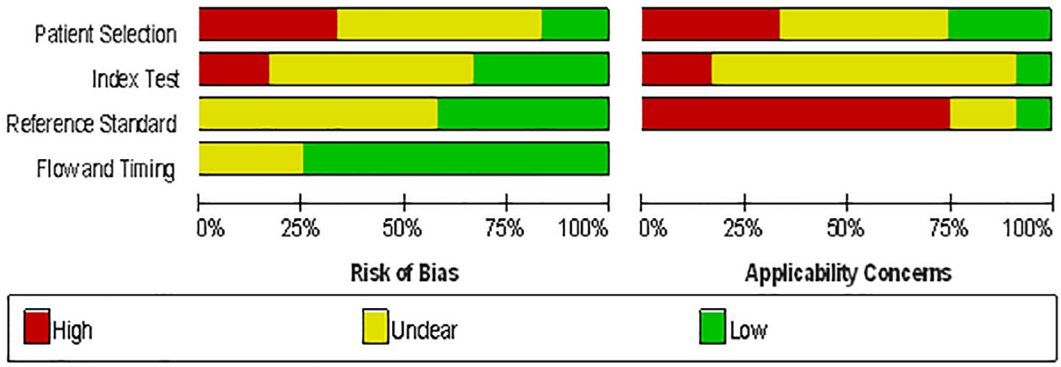

FIGURE 2 Bar graph of quality evaluation [Color figure can be viewed at wileyonlinelibrary.com]

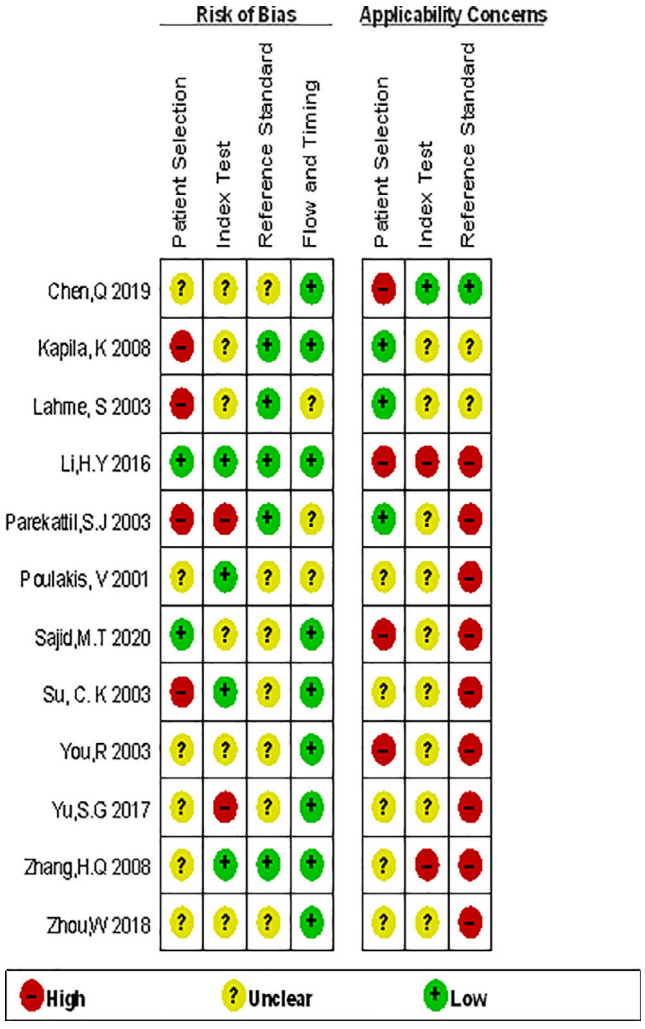

FIGURE 3 Summary chart of risk bias entries and adaptability [Color figure can be viewed at wileyonlinelibrary.com]

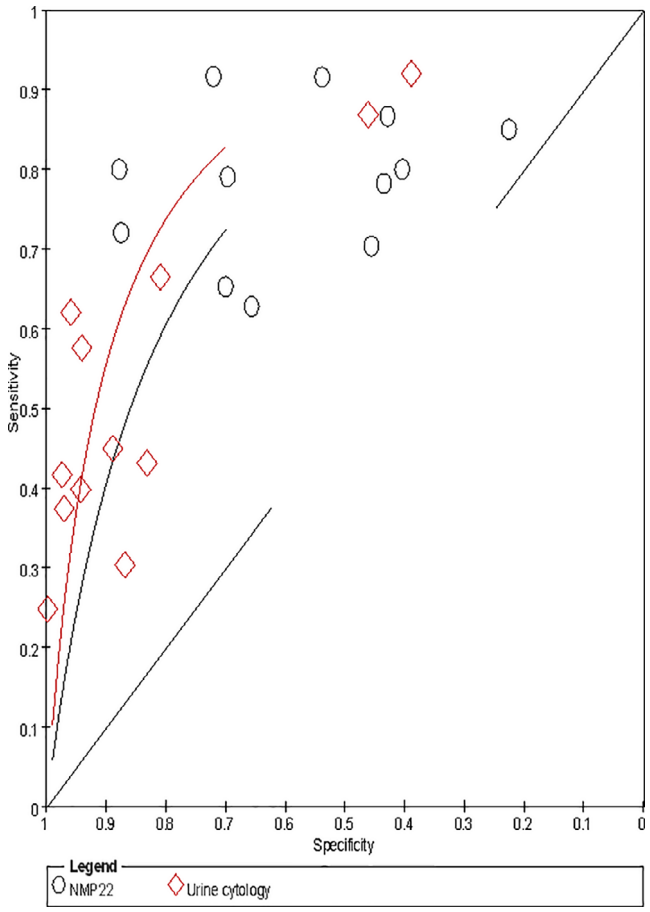

FIGURE 4 SROC curve of NMP22 and urine cytology [Color figure can be viewed at wileyonlinelibrary.com]

correlated with l-specificity), and the results show (Figure 4) that the sensitivity and specificity of NMP22 and UC are not significantly negatively correlated. If the SROC curve does not show a typical "shoulder-arm-like" distribution, there is no heterogeneity caused by threshold effect in NMP22 and UC.

2.4.2 | Non-threshold effects

Use Stata14 software to test the heterogeneity of other sources, the results show: NMP22 and UC combined sensitivity, specificity, +LR, −LR, DOR, and so forth. Q test $P < .01$, indicating the heterogeneity among the included studies is statistically significant, $I^2 > 50\%$, indicating that the heterogeneity is more obvious[11] (Figures 5–9), so the random effects model combined with effect size was used for meta analysis.

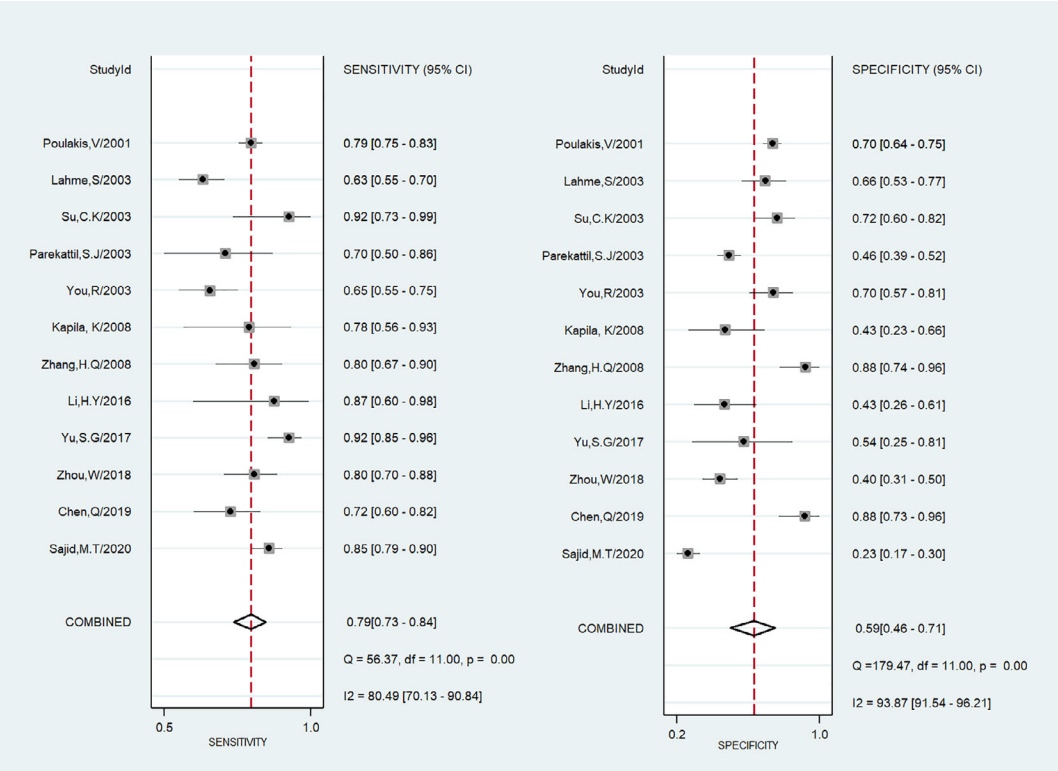

FIGURE 5 Forest plot of meta analysis of sensitivity and specificity of NMP22 in diagnosing bladder cancer [Color figure can be viewed at wileyonlinelibrary.com]

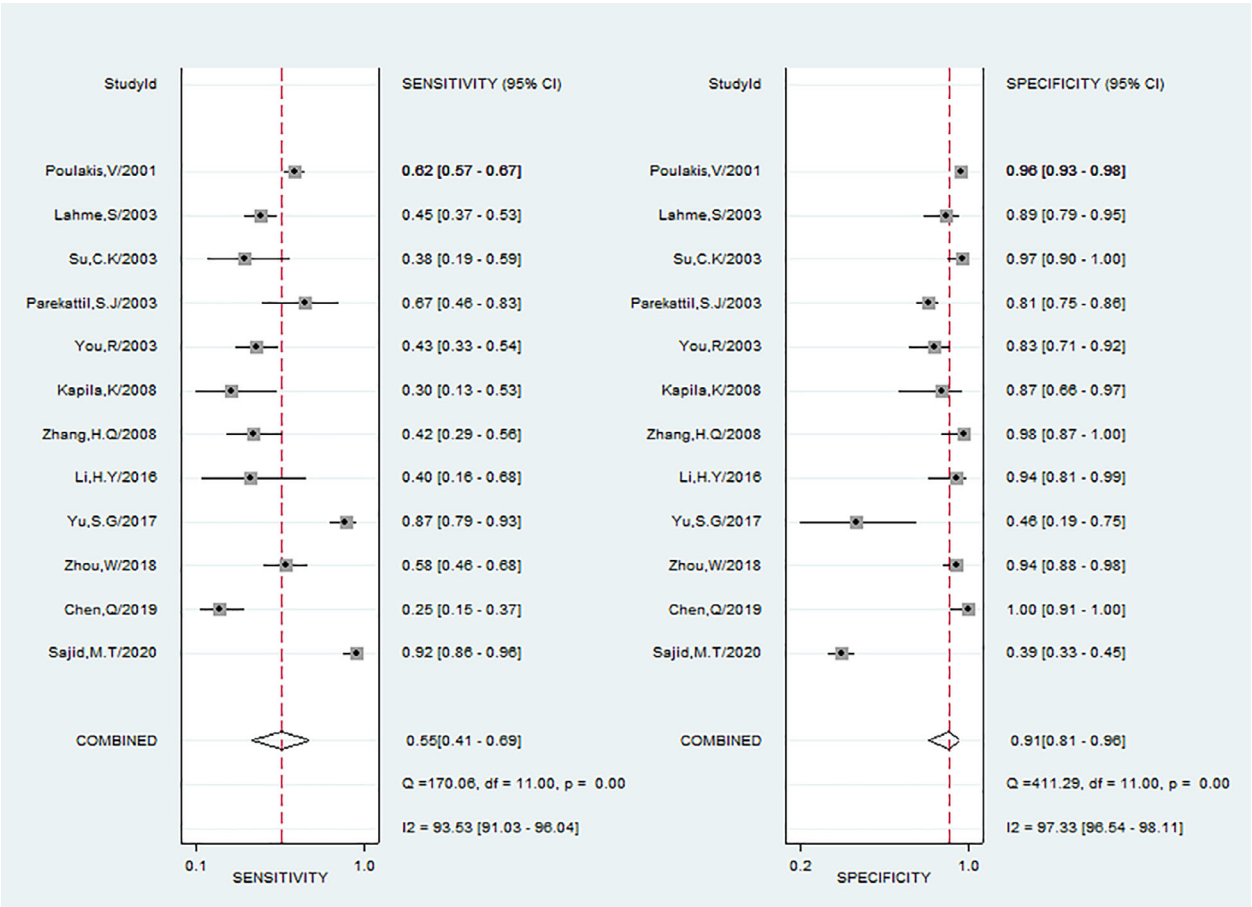

FIGURE 6 Forest plot of meta analysis of sensitivity and specificity of urine cytology for diagnosis of bladder cancer [Color figure can be viewed at wileyonlinelibrary.com]

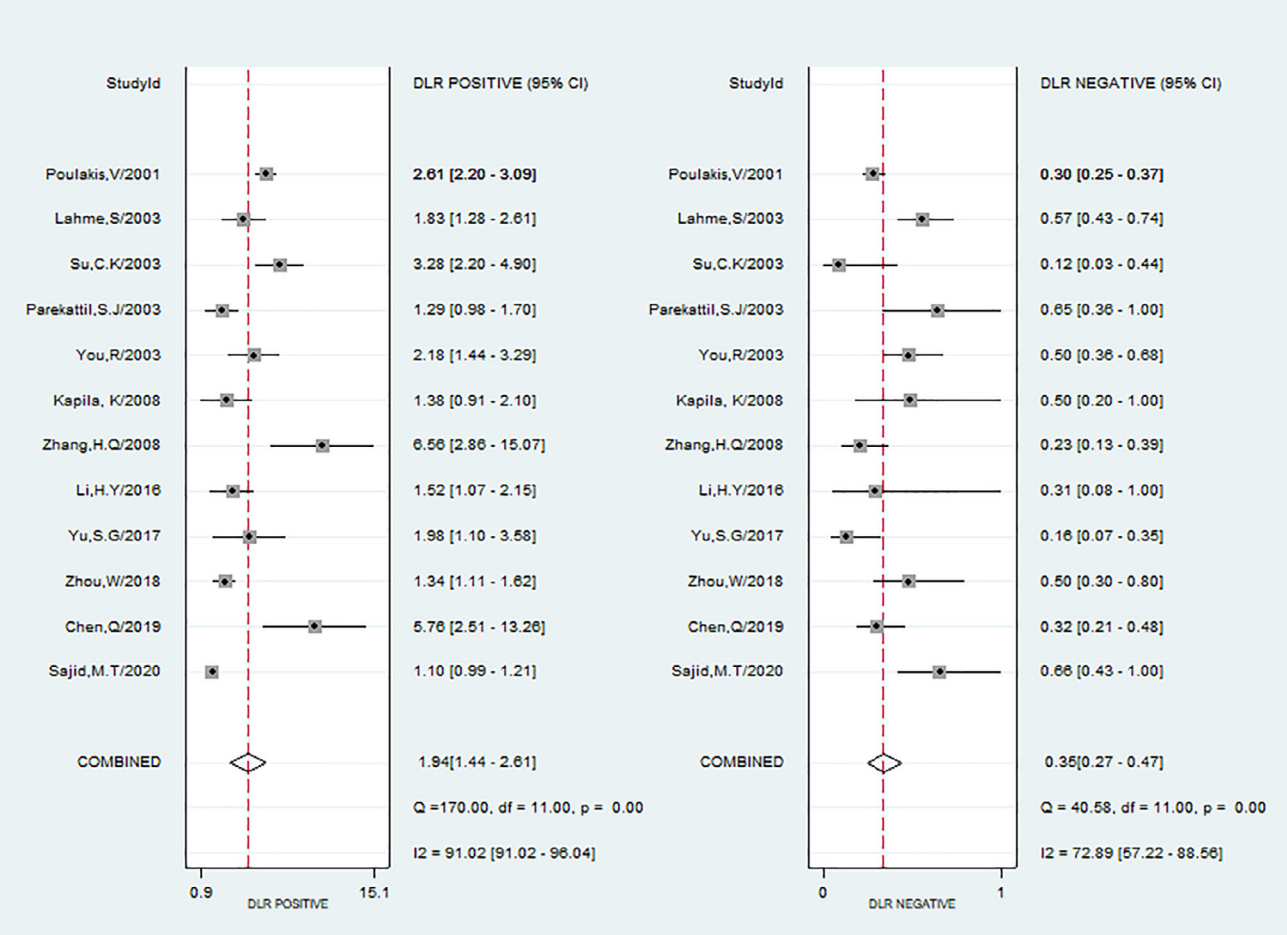

FIGURE 7 Forest plot of meta-analysis of the likelihood ratio of positive and negative NMP22 diagnosis of bladder cancer [Color figure can be viewed at wileyonlinelibrary.com]

2.5 | Results of statistical analysis

Since the heterogeneity test indicated that the effect sizes were heterogeneous across studies, meta-analysis was performed using a random effects model, and the total sensitivity of NMP22 and UC was calculated to be 0.79 (95% CI [0.73, 0.84]), 0.55 (95% CI [0.41, 0.69]), total specificity was 0.59 (95% CI [0.46, 0.71]), 0.91 (95%CI [0.81, 0.96]), +LR of 1.9 (95%CI [1.4, 2.6]), 5.9 (95%CI [3.3, 10.6]), −LR of 0.35 (95%CI [0.27, 0.47]), 0.49 (95%CI [0.38, 0.64]), with diagnostic odds ratios of 5 (95% CI [3, 9]), 12 (95% CI [7, 21]), and area under the SROC curve (AUC) of 0.79 (95% CI [0.75, 0.82]), 0.81 (95% CI [0.77, 0.84]), respectively. The larger the area under the SROC curve, that is, the closer the curve is to the upper left corner. It indicates that the inspection method has better diagnostic performance[12] . Comparing the area under the SROC curve (AUC) of the NMP22 test and UC, it can be assumed that the overall diagnostic efficiency of UC for bladder cancer is higher than that of NMP22 (Figures 4 and 9).

2.6 | Meta regressions

The results obtained by combining each subgroup separately, and the statistical test P value of the difference between each subgroup are given in Table 2. As can be seen in Figure 10 and Table 2, for the sensitivity, the prodesign variable ($P = .01$) and the subject variable ($P = .03$), the difference between the subgroups is statistically significant. According to the results of meta regression, we can conclude that its sensitivity is much affected by the type of study and the detailed description of the characteristics of the study population. Regarding the specificity, there was no statistically significant difference between the subgroups.

2.7 | Sensitivity analysis

In order to evaluate whether the results of this meta are stable, a sensitivity analysis was carried out. The 12 included studies were eliminated one by one, and the remaining studies were re-analyzed. The results show that there are no significant change in the amount of each effect before and after the elimination, indicating that the results of this study are stable.

2.8 | Evaluation of publication bias

The Deek funnel chart and asymmetry test of NMP22 and UC test were drawn by Stata14. The consequences of the asymmetry test were $P = .70$ and $P = .09$, so there was no obvious publication bias (Figure 11).

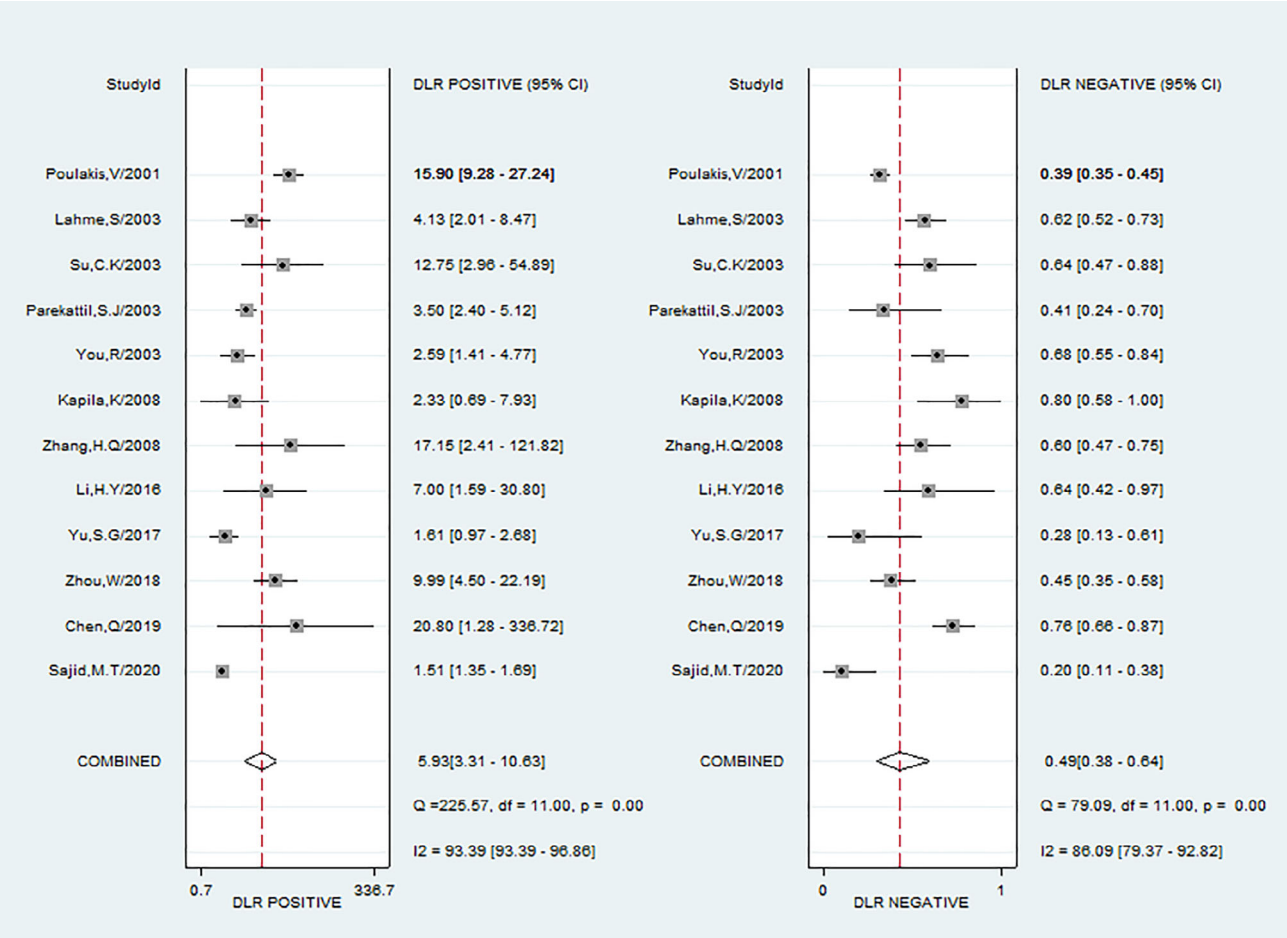

FIGURE 8 Forest plot of meta-analysis of likelihood ratios of positive and negative urinary cytology for diagnosis of bladder cancer [Color figure can be viewed at wileyonlinelibrary.com]

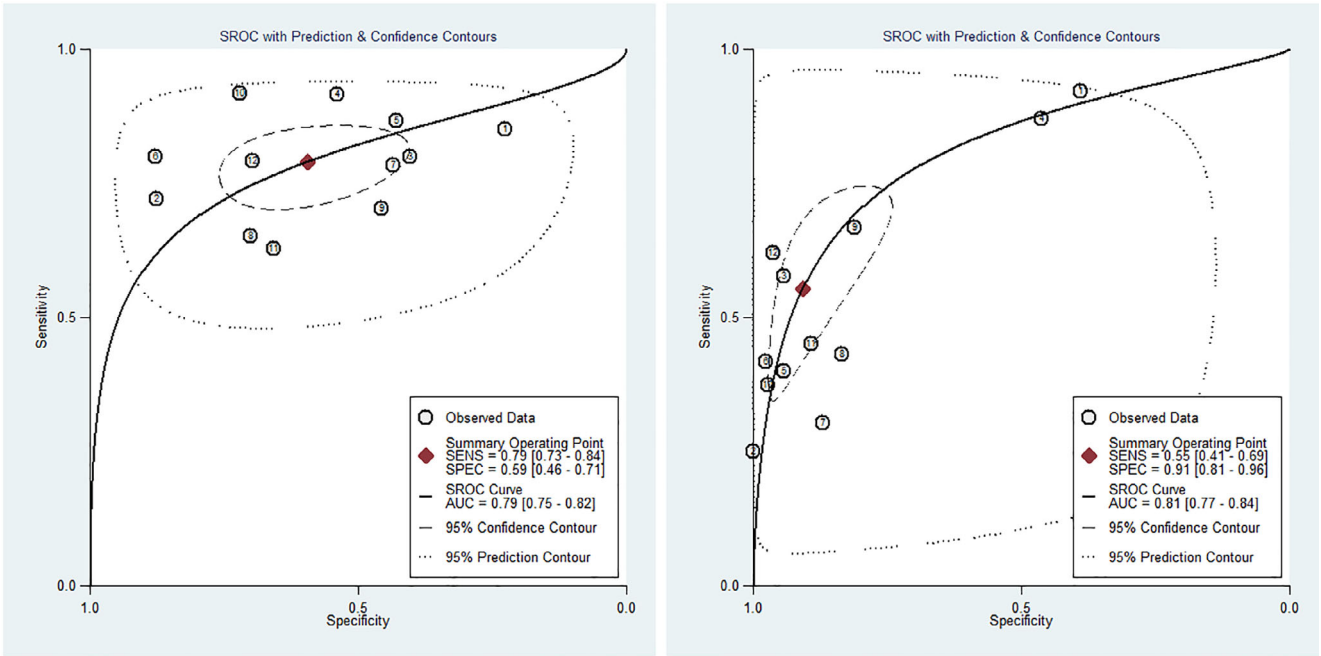

FIGURE 9 Comparison of the area under the curve of NMP22 (left) and urine cytology (right) SROC curve [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Single factor regression results of sensitivity and specificity

Parameter	Category	Studies (*n*)	Sensitivity	p1	Specificity	p2
Prodesign	Yes	7	0.79 (0.72–0.85)	0.01	0.66 (0.51–0.81)	0.51
	No	5	0.79 (0.70–0.88)		0.50 (0.32–0.68)	
Index	Yes	11	0.79 (0.73–0.85)	0.19	0.58 (0.45–0.71)	0.55
	No	1	0.79 (0.64–0.94)		0.70 (0.34–1.00)	
Reftest	Yes	1	0.79 (0.56–1.00)	0.58	0.43 (−0.02–0.89)	0.48
	No	11	0.79 (0.73–0.84)		0.61 (0.48–0.73)	
Subject	Yes	8	0.82 (0.77–0.87)	0.03	0.62 (0.48–0.76)	0.62
	No	4	0.73 (0.65–0.82)		0.50 (0.29–0.71)	

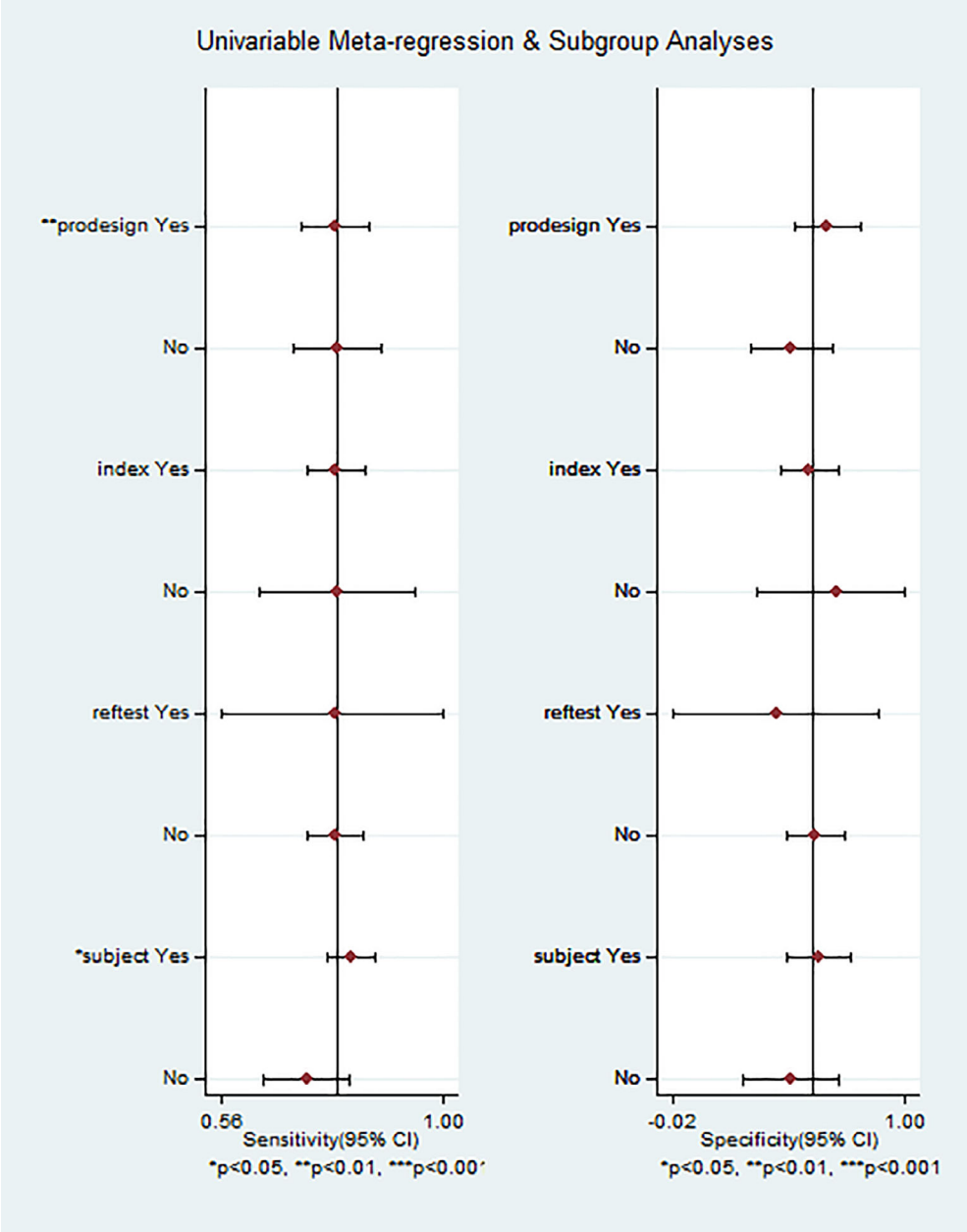

FIGURE 10 Univariable meta-regression and subgroup analyses [Color figure can be viewed at wileyonlinelibrary.com]

2.9 | Clinical application value

Draw Fagan charts, set the pre-test probability of 58%, and then supplement with the detection of NMP22 and UC. When the two tests are positive, the accuracy of diagnosing bladder cancer is 73% and 89%, respectively; When the test is negative, the accuracy of diagnosing bladder cancer is 33% and 40% (Figure 12), indicating that the two have good accuracy in diagnosing bladder cancer.

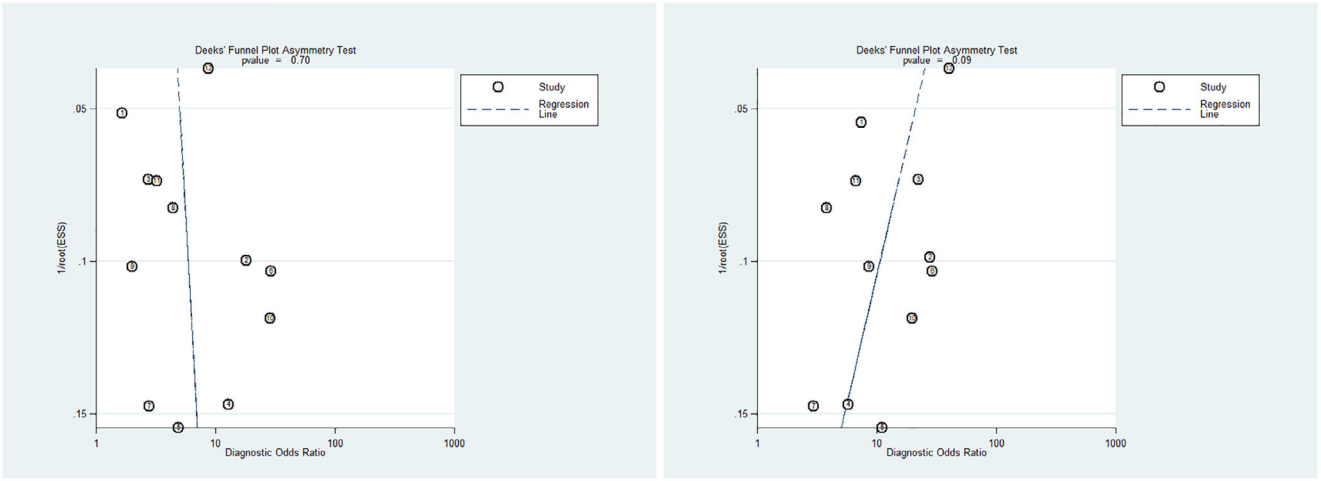

FIGURE 11 Deek funnel chart and asymmetry test of NMP22 (left) and urine cytology (right) [Color figure can be viewed at wileyonlinelibrary.com]

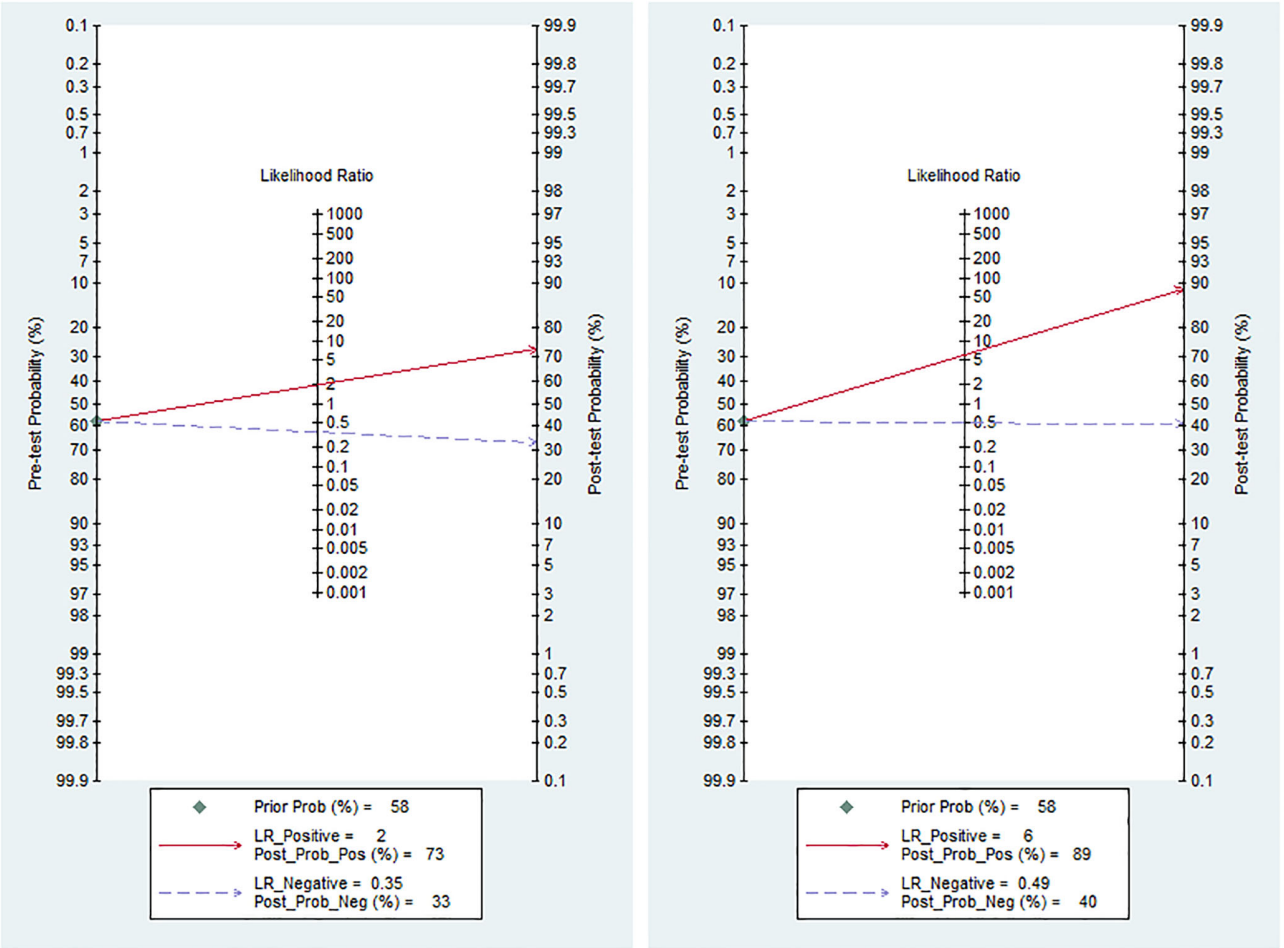

FIGURE 12 Pre-test probability and post-test probability calculation diagram of NMP22 (left) and urine cytology (right) [Color figure can be viewed at wileyonlinelibrary.com]

3 | DISCUSSION

Bladder cancer is part of the widespread malignancy of the genitourinary system in our country, and its morbidity and mortality rates are extremely high in our country. At present, common screening methods for bladder tumors have their own advantages and disadvantages. The current research results on the diagnostic value of NMP22 are not the same. Based on this, this study systematically analyzed the literature data of NMP22 and UC in the diagnosis of bladder neoplasms to clarify its diagnostic value for bladder neoplasms and provide a theoretical basis for clinical diagnosis and treatment of bladder neoplasms.

We used Stata14 and Revman5.3 software to systematically evaluate the value of NMP22 and UC in the diagnosis of bladder neoplasms. The results showed that the sensitivity of NMP22 and UC were 0.79 and 0.55, the specificity was 0.59 and 0.91, the diagnostic odds ratio was 5 and 12, and the area under the SROC curve (AUC) was 0.79 and 0.81. It can be seen that NMP22 and UC are of medium efficiency in diagnosing bladder tumors, and the former is slightly lower than the latter, the sensitivity is higher than the latter, and the specificity is significantly lower than the latter. However, some studies have shown that NMP22 had better specificity than sensitivity. For example, the results of both Rhijn, Bwgv et al., and MT Sajid et al., showed that the sensitivity of NMP22 was lower than the specificity, the reason may be related to the different selected thresholds between the studies and the differences in the number of patients.[13,14] In the SF Shariat study, NMP22 predicted bladder cancer with equal sensitivity and specificity at a threshold of 6.5 U/ml, and was preferable to the 10 U/ml cut-point across all pathological stages and grades.[15]

From the results of meta analysis alone, the diagnostic efficiency of NMP22 is not high, and it cannot replace cystoscopy and pathological examination to diagnose and screen bladder tumors alone; but from the perspective of clinical application value, the pre-test probability is set to 58%, and the pre-test probability is set to 58%. The Fagan chart shows that when the two tests are positive, the accuracy of diagnosing bladder cancer is 73% and 89%, respectively; when the two tests are negative, the accuracy of diagnosing bladder cancer is 33% and 40%, respectively (Figure 12), suggesting that the two have good accuracy in diagnosing bladder cancer and have good clinical application value, so they are of great significance as a non-invasive examination for bladder tumor screening.

Among the 12 documents included in this study, there are some variations in sensitivity and specificity, which may be attributed to the following reasons:

1. Most of the 12 documents included did not carry out or mention whether random sampling was carried out;
2. Part of the research experimental group included patients with a clear diagnosis, and the control group included suspected patients or even normal people, urinary tract infections, other benign diseases, and so forth;
3. Some studies did not use or mention whether blinding was used during the research process;
4. Different experimental designs and test methods in each study, that is, differences in methodological quality.

In addition, this study also has the following limitations:

1. The quality of the literature: (a) The number of included literature is small, and the sample size of each study is small; (b) The study only includes articles published in Chinese and English, and there is a certain selection bias; (c) Although an extensive search strategy was adopted, the Deek funnel chart and asymmetry test showed no obvious publication bias, but there are still some gray literatures that cannot be obtained, so the potential publication bias cannot be ruled out; (d) In the included studies, the population age, age, and asymmetry cannot be ruled out. The descriptions of gender and testing methods are relatively good, but there are few reports on race, medical environment, and so forth.
2. The heterogeneity of the literature: The results of this study suggest that there is no heterogeneity caused by the threshold effect, but there is heterogeneity caused by other reasons (Q test $P < .01$, $I^2 > 50\%$). The meta-regression found that the heterogeneity is mainly caused by the type of experimental research included in the study and whether the population characteristics are described in detail.
3. Due to the limitation of the information included in the literature, the sensitivity of the various pathological grades and stages of bladder cancer, the initial and recurrent tumors, and the combined analysis were not performed. NMP22 and urinary cytology were used to analyze the initial and recurrence of bladder cancer. The diagnostic value of this method needs to be further studied and analyzed.

The advantages of this study are as follows:

1. Strictly follow the inclusion criteria and exclusion criteria to screen the literature, and the quality of the included literature is generally better;
2. Perform meta regression, sensitivity analysis and publication bias detection, and further evaluation and analysis results are more stable, reliable;
3. Drawing Fagan chart shows that NMP22 and UC have good clinical application value.

Yang Qing et al.,[16] studied the combined application of NMP22 and UC to detect hematuria specimens, and the results showed that 42% of missed tumors were found in UC, and 37% of tumors that were missed in cytology were found in NMP22. In this experiment, the sensitivity of NMP22 combined with urine exfoliated cytology was 91.7%, which was significantly better than NMP22 and UC alone, but the specificity decreased. Adding the NMP22 test to the MME's marking standards can improve diagnostic accuracy.[17] Research by Chen Qiang et al., showed that the sensitivity of NMP22 to diagnose the recurrence of patients with low- and medium-risk bladder neoplasms is significantly better than that of UC.[18] Research by Binnur

Önal et al., showed that the NMP22 values displayed higher sensitivity for low-grade UC while cytology was highly sensitive and specific for detection of high-grade UC. Combining urine NMP22 assay with atypical cytology improved sensitivity for detection of recurrent UC.[19]The results of Narmada PG et al.,[20] showed that adding NMP22 to UC can improve the sensitivity of recurrence detection in patients with superficial transitional cell bladder cancer, which is comparable to that of patients with negative NMP22 test results. Compared with patients who test positive for NMP22, the risk of recurrence within 1 year is higher (9.57 times).

Detection of UC relies on the non-adherence of high-grade urothelial cells, which are readily sloughed into the urethra for microscopy. However, low-grade urothelial tumor cells showed substantial cytomorphological overlap with benign urothelial cells and were more cohesive.[21] Therefore, UC has poor sensitivity and specificity for low-grade urothelial neoplasms (LGUN) and high sensitivity and specificity for high-grade urothelial carcinoma (HGUC). Therefore, UC is mainly used to detect high-grade lesions. Because of the difficulty in detecting low-grade urothelial tumors in UC specimens, the performance of UC to detect all urothelial carcinomas is generally inferior to that of only high-grade lesions.[22,34] At the same time, the naturally shed cells in the urine are consistently exposed to the toxic substances in the urine, which can be also given an impact on the results of the study. Prior to the implementation of The Paris System for Reporting Urinary Cytology (TPS), most studies focused on detecting all urothelial cancers regardless of tumor grade, whereas after TPS was implemented, it focused on diagnosing high-grade rather than low-grade urinary epithelial carcinoma, so it is difficult to directly compare the results before and after the implementation of TPS. There are several studies investigating the use of TPS in upper urinary tract specimens showing that the implementation of TPS improves the detection performance of UC and increases the identification of high-grade lesions.[22,35] This may be the reason why most studies only focus on UC in urothelial carcinoma, and few separate analyses of low-grade and high-grade lesions. Then, it is not appropriate to simply compare UC, which is mainly used to detect high-grade lesions, with other auxiliary tests that can detect both low-grade and high-grade lesions. Therefore, we should actively look for combined detection indicators to make up for the deficiency of UC in detecting low-grade lesions, rather than simply comparing the sensitivity and specificity of UC with additional auxiliary tests.

In summary, NMP22 has a certain value in screening for bladder tumors. It is more sensitive to the diagnosis of recurrence in patients with moderate and low-risk bladder neoplasms than urinary cytology, which has important clinical significance. Although its overall sensitivity is better than UC, its specificity is not as good as UC, and it is still difficult to replace cystoscopy and UC. The two can be combined to improve the diagnostic efficiency of bladder cancer. As the research content continues, NMP22 will have a broader application prospect as a clinical tumor marker for screening, postoperative monitoring and follow-up of bladder neoplasms.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Wang Jie: Find a research direction; design research; collect and organize data; analyze data individually; writing–original draft; writing–review and editing. Zhao Xi: Study conceptualization; collect and organize data; analyze data individually; writing–review and editing. Jiang Xiaolei: Study conceptualization; data curation; study supervision. Yuan Qiang: Collect relevant literature; study conceptualization; study supervision; resolve existing differences. Li Jiabing: Study conceptualization; study supervision; resolve existing differences; writing–review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jiabing Li https://orcid.org/0000-0002-7772-9292

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