Systematic Review and Meta-Analysis

Medicine

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Diagnostic accuracy of MUC7 expression for bladder cancer

A systematic review and meta-analysis

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Abstract

Background: There have been many studies on MUC7 and bladder cancer (BC) that have been published; however, all sample sizes were not enough which led to their conclusions being based on small samples. Therefore, this meta-analysis aims to systematically analyze the diagnostic value of MUC7 for bladder cancer and provide a scientific basis for the diagnosis of bladder cancer.

Methods: To obtain relevant literature on MUC7 diagnosed bladder cancer, databases such as PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang data, Chongqing VIP, and Chinese Biomedical Literature Database were searched from the establishment of the database to July 11, 2023. According to established inclusion and exclusion criteria, literature was screened and data were extracted. The Quality Assessment of Diagnostic Accuracy Studies 2 was used to evaluate the risk of bias and applicability of included literature. Meta-disc1.4 and Stata12.0 software were used for Meta-analysis.

Results: Twelve studies were included, including728 BC patients and 458 non-BC controls. The pooled sensitivity and pooled specificity were 0.74 (95% confidence interval [CI]: 0.71–0.77) and 0.92 (95% CI: 0.90–0.95), respectively. The pooled negative likelihood ratio was 0.27 (95% CI: 0.20–0.36), and the pooled positive likelihood ratio was 9.58 (95% CI: 5.40–17.00). The diagnostic odds ratio was 40.95 (95% CI: 20.31–82.59), and the area under the curve was 0.91 in the overall summary of the receiver operating characteristic curve.

Conclusion: MUC7 might be a potential biomarker for diagnosing BC. However, more large sample and multicenter studies are needed to prove whether it can be used in clinical diagnosis.

Abbreviations: AUC = area under curve, BC = bladder cancer, CI = confidence interval, DOR = diagnostic odds ratio, NMIBC = non-muscle-invasive bladder cancer, NLR = negative likelihood ratio, PLR = positive likelihood ratio, RT-PCR = reverse transcription polymerase chain reaction, SEN = sensitivity, SPE = specificity, SROC = summary of characteristic curve.

Keywords: bladder cancer, diagnosis, meta-analysis, MUC7, urinary bladder neoplasms

1. Introduction

According to the latest epidemiological survey, bladder cancer (BC) ranks as the 10th most commonly diagnosed cancer worldwide, accounting for approximately 573,000 new cases and 213,000 deaths.[1] While tobacco smoking remains the most significant global risk factor for bladder cancer, regions in North and parts of sub-Saharan Africa have shown Schistosoma haematobium infection to be a major carcinogen. In other areas, occupational exposure to aromatic amines, aluminum industries, and arsenic-contaminated drinking water also play important roles in the development of bladder cancer.[2]

BC diagnoses reveal that over 75% of patients have non-muscle-invasive bladder cancer (NMIBC), with a smaller number having muscle-invasive bladder cancer, and distant metastasis being rare. NMIBC is usually treatable with transurethral resection of bladder tumors and generally has a better prognosis than muscle-invasive bladder cancer.[3] However, NMIBC has the potential to rapidly invade the muscle layer, leading to a lethal condition with limited treatment options.[4] Hence, early diagnosis and long-term prognosis monitoring are crucial for effective treatment and improved outcomes. Currently, the main methods for diagnosing bladder cancer are cystoscopy and urine cytology.[5] While these approaches are widely used,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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they suffer from several drawbacks. Cystoscopy is expensive and invasive, potentially causing trauma and urinary tract infections.[6] Additionally, its sensitivity in diagnosing carcinoma in situ is low, and the accuracy of results depends on the operator's experience.[7] On the other hand, urine cytology is noninvasive and highly specific, but it exhibits low sensitivity (around 35%) in detecting low-grade bladder cancer.[8] Moreover, a negative urine cytology result does not rule out the presence of a tumor, as it can be influenced by factors such as a low cell count, urinary tract infection, or stones.[9] Consequently, there is a pressing need to develop a noninvasive, highly sensitive, and specific method for diagnosing bladder cancer.

Mucins are large glycoprotein macromolecules expressed in glandular epithelial cells of various tissues, including the urinary tract, respiratory tract, and gastrointestinal tract. The diagnostic potential of MUC7 in detecting bladder cancer was first investigated by Retz M et al[10], who utilized the reverse transcription polymerase chain reaction (RT-PCR) technique to measure its expression in bladder cancer tissue. This discovery was subsequently confirmed in 2003 by Okegawa T, who further demonstrated the diagnostic value of urine MUC7 in bladder cancer.[11] Since then, several researchers have studied the diagnostic value of MUC7 in detecting bladder cancer, yielding some promising results.

One recent study reported that MUC7 exhibited a sensitivity of 80% and a specificity of 100% in detecting urine samples from bladder cancer patients. Despite these encouraging findings, the application of MUC7 as a diagnostic biomarker for bladder cancer still requires further validation. The limited number of clinical trials, variations in patient ethnicity, and insufficient study populations necessitate a systematic assessment of its diagnostic value before widespread adoption.

In order to comprehensively investigate the diagnostic efficacy of MUC7 in bladder cancer patients, we conducted a systematic review with meta-analysis, incorporating data from 12 original studies. Through this analysis, we aim to consolidate the relevant research findings and provide more precise estimates of MUC7's diagnostic value in the context of bladder cancer detection.

2. Methods

2.1. Literature search

This meta-analysis adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[12] Two independent investigators conducted a thorough search across multiple databases, including PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang data, Chongqing VIP, and Chinese Biomedical Literature Database databases. The retrieval period extended from the inception of the libraries to July 11, 2023. The search was limited to articles published in either Chinese or English.

A comprehensive search strategy was employed, incorporating the following keywords: ("urinary bladder neoplasm" or "bladder neoplasm" or "bladder tumor" or "urinary bladder cancer" or "malignant tumor of urinary bladder" or "cancer of the bladder" or "bladder cancer" or "cancer of bladder" or "urothelial carcinoma") and ("MUC7" or "Mucin7") and ("sensitivity" or "specificity" or "diagnostic" or "detection" or "ROC curve" or "ROC analyses" or "ROC analysis" or "receiver operating characteristic").

To ensure the inclusion of all relevant studies, the reference lists of eligible articles were also manually searched to identify additional relevant literature.

2.2. Eligibility criteria

2.2.1. Inclusion criteria. The studies included in this meta-analysis primarily focused on evaluating the diagnostic value of MUC7 for BC. The following inclusion criteria were applied:

(1) BC diagnosis was based on histological examination, ensuring the accuracy of the disease identification.
(2) The control groups consisted of non-bladder cancer patients and/or normal individuals, allowing for a proper comparison.
(3) MUC7 expression was measured in both bladder cancer patients and control groups, ensuring consistency in the evaluation.
(4) Sufficient data were available to construct a complete 4-grid table, which is necessary for conducting the meta-analysis.
(5) The studies were published in either English or Chinese, ensuring comprehensiveness in the literature search.

2.2.2. Exclusion criteria. The exclusion criteria were as follows:

(1) Case reports, meeting reports, or review articles were excluded, as they may not provide sufficient original data for the analysis. Animal or cell experiments;
(2) Animal or cell experiments were excluded, as the focus was on clinical studies involving human subjects.
(3) Studies that duplicated previous publications were excluded to avoid bias and repetition of data.
(4) Studies with incomplete clinical data were also excluded to ensure the reliability and robustness of the analysis.

2.3. Study selection and quality assessment

During the screening process, 2 investigators independently reviewed the retrieved literature, and any disagreements that arose were resolved through consensus. The following data were extracted from the included studies: True positives; False positives; False negatives; True negatives; and The total number of patients enrolled in each study. Additional data were also collected, including: The name of the first author; Publication year; Country; Detection method and; Gold standard. Furthermore, the quality of each included study was assessed using The Quality Assessment of Diagnostic Accuracy Studies 2 tool, which helps evaluate the methodological quality and risk of bias in diagnostic accuracy studies.[13] The Quality Assessment of Diagnostic Accuracy Studies 2 tool consists of 2 main parts: the assessment of risk of bias and concerns regarding applicability. The risk of bias assessment includes 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain comprises 7 items, and each item is evaluated with "yes," "no" or "unclear" responses. A "yes" response indicates a low risk of bias, while "no" or "unclear" responses indicate a high risk of bias. The concerns regarding applicability assessment include 3 domains: patient selection, index test, and reference standard. Each domain is evaluated with "high," "low" or "unclear" responses, indicating the level of concern regarding the applicability of the study. ReviewManager5 .3 (https://training.cochrane.org/online-learning/core-software/revman) was used to perform the process.

2.4. Statistical analysis

This meta-analysis follows internationally recommended criteria for conducting diagnostic meta-analyses.[14] Meta-disc1.4 software[15] and Stata (version 15.0; StataCorp, LLC) software were applied to analyze and integrate the extracted data. Revman 5.3 (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration) was used to evaluate the quality of the included literature. Sensitivity (SEN), specificity (SPE), negative likelihood ratio (NLR), positive likelihood ratio (PLR) and

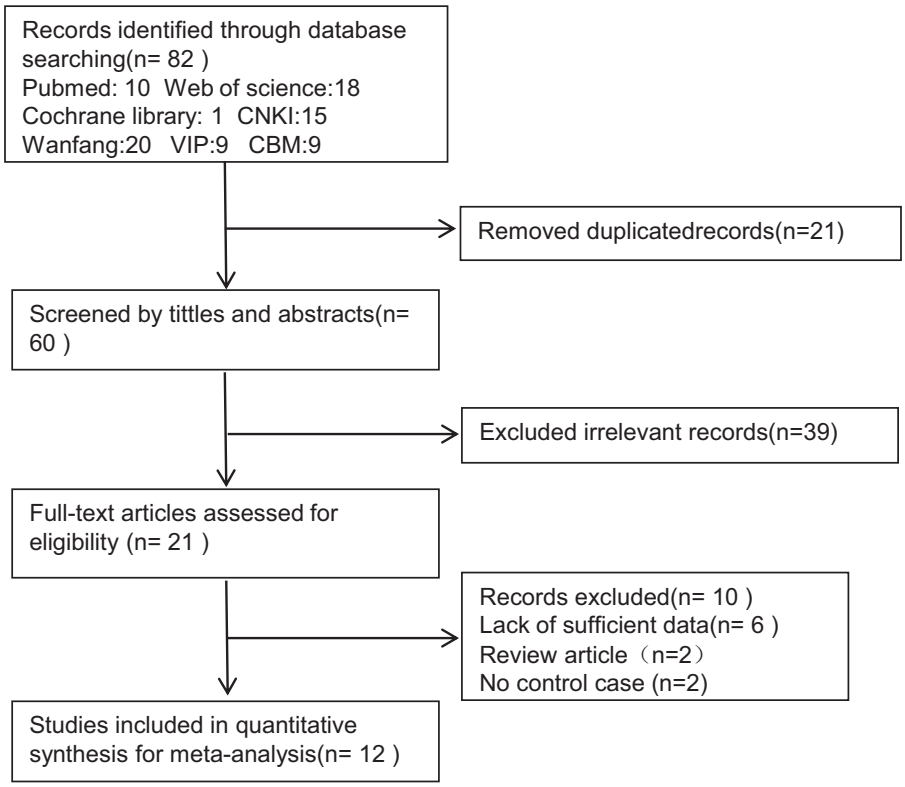

Figure 1. Flow diagram of literature search for this meta-analysis.

Table 1

Characteristics of the included studies.

First Author	Year	Country	Method	Sample type	Patient number	Control number	TP	FN	FP	TN
Kinjo M[26]	2004	Japan	Nested RT-PCR	Blood	38	18	18	20	0	18
Yu-Lin Ren[21]	2010	China	IMC	Tissue	50	6	37	13	0	6
Okegawa T[11]	2003	Japan	Nested RT-PCR	Urine	65	45	44	21	2	43
M Retz[10]	1998	Germany	RT-PCR	Tissue	17	16	13	4	1	15
Xiao-Yong Pu[22]	2007	China	RT-PCR	Urine	115	58	72	43	2	56
M Retz[27]	2003	Germany	Nested RT-PCR	Urine	50	80	33	17	16	64
Zhen-Xiang Lin[19]	2019	China	RT-PCR	Urine	75	58	60	15	0	100
Chen-Ying Huang[20]	2011	China	RT-PCR	Urine	60	30	53	7	3	27
Rong-Rong Zhang[23]	2008	China	RT-PCR	Urine	52	34	44	8	5	29
Hong Liao[24]	2006	China	RT-PCR	Urine	42	40	36	6	2	38
Di Xiao[25]	2006	China	Nested RT-PCR	Urine	68	25	42	26	3	22
CHEN Kaixun[28]	2021	China	Elisa	Urine	96	48	86	10	4	44

Elisa = enzyme-linked immunosorbent assay, FN = false negatives, FP = false positives, IMC = immunohistochemistry, RT-PCR = reverse transcription polymerase chain reaction, TN = true negatives, TP = true positives.

95% confidence interval (CI) were calculated from the extracted true positives, false positives, true negatives, and false negatives values. Summary of characteristic curve (SROC) curve[16,17]was constructed based on a bivariate regression approach, was used to evaluate the diagnostic accuracy of MUC7. Heterogeneity was tested by Cochran Q test and I-square statistical. When I^2 > 50% or P < .1, it means that there is significant heterogeneity, and the random effect model was applied. On the contrary, when I^2 < 50% or P > .1, the fixed-effect model was used. Whether the heterogeneity could be explained by a threshold effect was detected by ROC plane and the spearman correlation coefficient.[14] When there was a threshold effect, SEN and SPE were an inverse correlation, which could cause the typical "shoulder arm " distribution of ROC plane distribution. Similarly, when Spearman correlation analysis showed a strong positive correlation (P < .05), it meant the existence of a threshold effect. Meta-regression and subgroup analysis were performed to analyze the sources of heterogeneity. Begg funnel plot test was conducted to evaluate the publication bias.[18]

3. Results

3.1. Search results and selected studies

The results of the literature screening process for the current study were presented in Figure 1. Initially, 82 relevant articles were obtained from the database search, out of which 21 duplicates were excluded, leaving 60 unique studies for further evaluation. Two reviewers assessed the titles and abstracts of these studies and reached a consensus to exclude 39 irrelevant studies. Subsequently, 21 potentially eligible studies were selected for full-text examination.

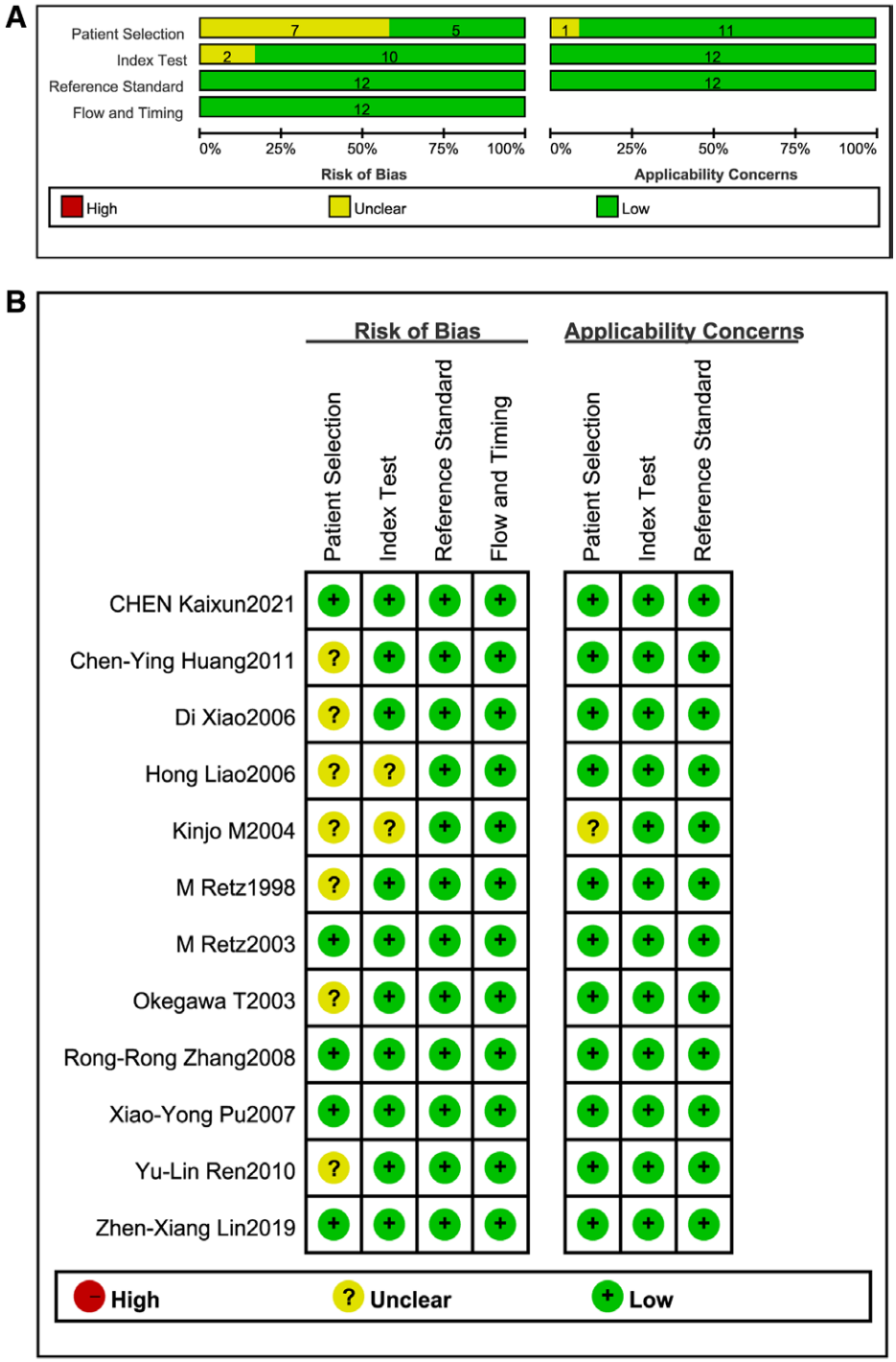

Figure 2. QUADAS-2 assessments for the risk of bias of the included studies. (A) Risk of bias and applicability concerns graph. (B) Risk of bias and applicability concerns summary. QUADAS-2 = quality assessment of diagnostic accuracy studies 2.

After a thorough review of the full-text articles, 10 studies were excluded from the analysis. The reasons for their exclusion were either a lack of complete data or incomplete descriptions of the trials. As a result, the final number of studies included in the analysis was 12.

Ultimately, a total of 12 eligible studies[10,11,19–28]were included in the meta-analysis.

3.2. General character of the included studies

Table 1 provides a summary of the general data and main characteristics of the studies included in the analysis. The selected studies were published between 1998 and 2023 and were conducted in Germany, Japan, and China. In total, the studies involved 728 patients with bladder cancer and 458 normal controls. Various methods were employed in these studies, including immunohistochemistry, RT-PCR, nested RT-PCR, and enzyme-linked immunosorbent assay.

The sample types used in all the included studies were categorized as follows: urine samples constituted 75% of the cases, tissue samples accounted for 16.7%, and blood samples represented 8.3%. These samples were collected from the participants to assess the diagnostic accuracy of MUC7 in detecting bladder cancer.

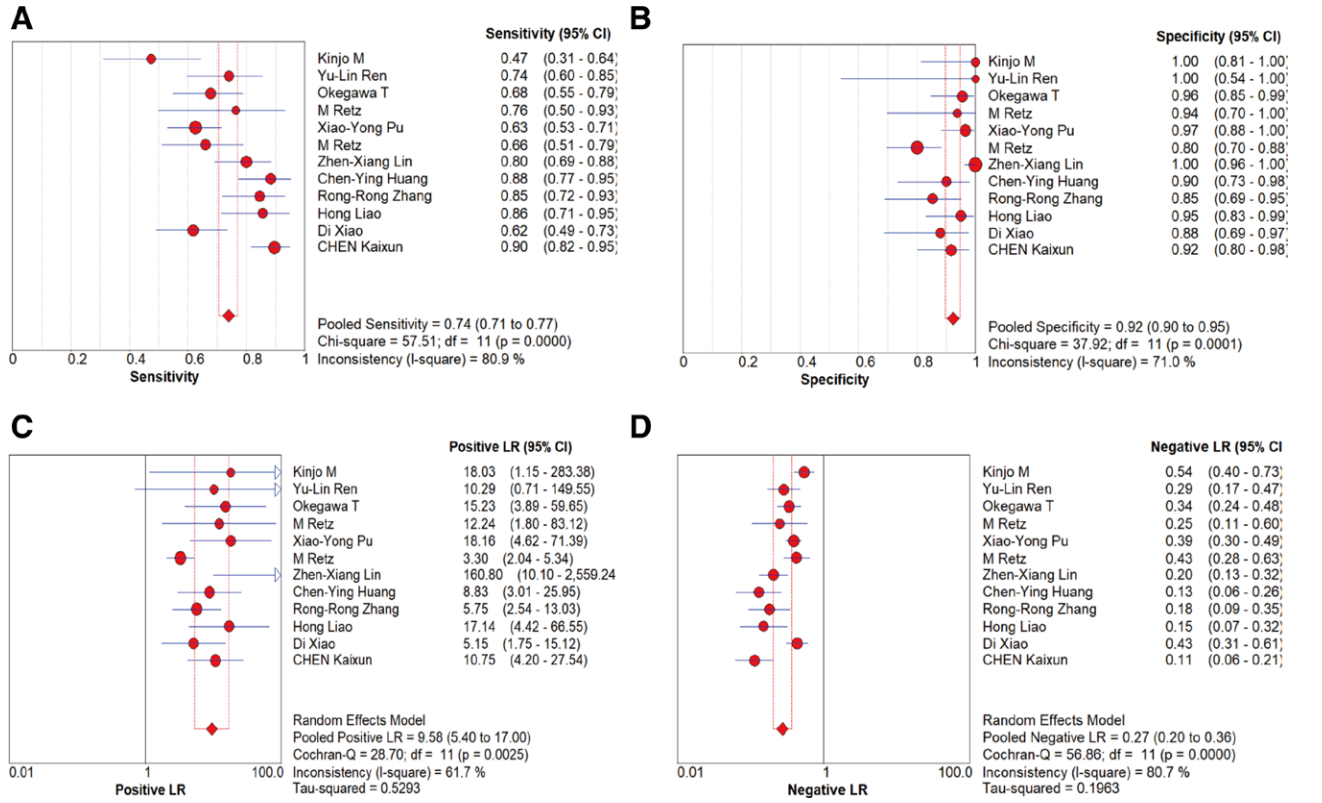

Figure 3. Forest plots of pooled, (A) sensitivity, (B) specificity, (C) positive LR, and (D) negative LR of MUC7 for the diagnosis of BC. BC = bladder cancer.

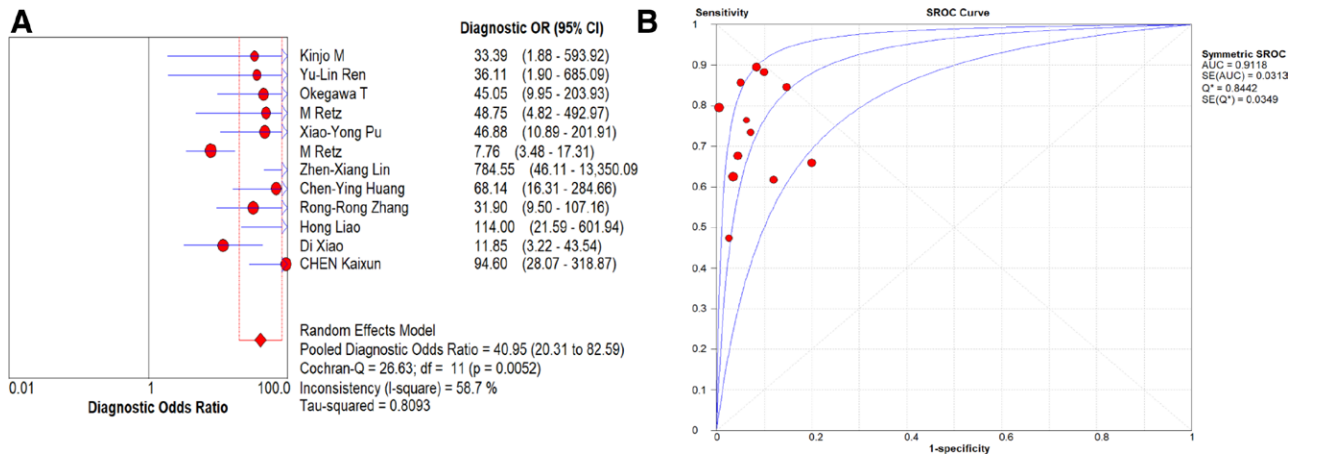

Figure 4. (A) Forest plots of pooled of Diagnostic Odds Ratio and (B) SROC Curve of MUC7 for the diagnosis of bladder cancer. SROC = summary of characteristic curve.

Table 2

The pooled value of MUC7 for the diagnosis of bladder cancer.

	Test of association		Test of heterogeneity			
Parameter	**Estimates**	**95% CI**	**Q**	***P* value**	***I*² (%)**	**Model**
Sensitivity	0.74	0.71–0.77	57.51	<.01	80.9	Random
Specificity	0.92	0.90–0.95	37.92	<.01	71.0	Random
Positive LR	9.58	5.4–17.0	28.7	<.01	61.7	Random
Negative LR	0.27	0.20–0.36	56.86	<.01	80.7	Random
DOR	40.95	20.31–82.59	26.63	<.01	58.7	Random

CI = confidence interval, DOR = diagnostic odds ratio, LR = likelihood ratios.

3.3. Quality of articles

The quality evaluation results of the included studies are presented in Figure 2. The bar graph (Fig. 2A) illustrates that the overall quality of the included studies was relatively high. However, there were some potential sources of bias, mainly stemming from the patient selection in certain studies. Figure 2B provides a detailed list of each study's performance in the quality assessment.

3.4. Pooled diagnostic values

Because there is heterogeneity between studies, a random-effects model was used to incorporate the effects. Forest plots were used to summarize the pooled SEN, SPE, NLR, PLR, and

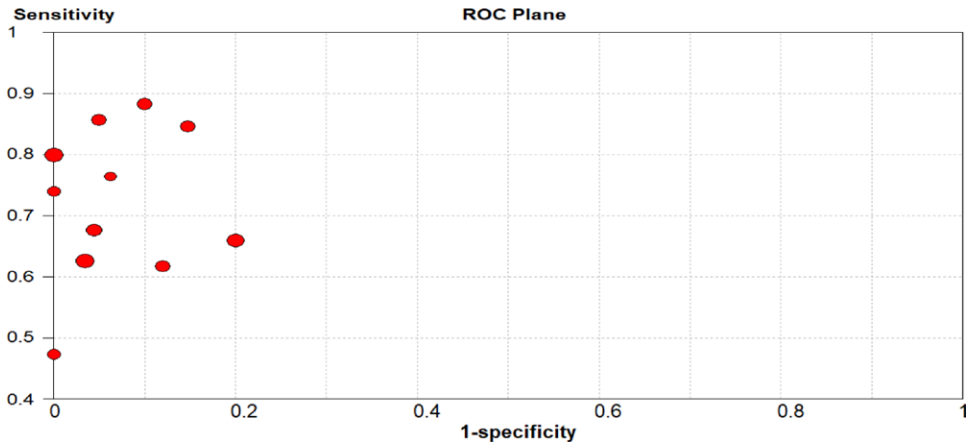

Figure 5. ROC Plane of MUC7 for the diagnosis of bladder cancer.

Table 3

The meta-regression analysis of MUC7 in the diagnosis of bladder cancer.

Variable	Coeff	Std.Err	*P* value	RDOR	[95% CI]
sampletype	0.114	0.6393	.86	1.12	(0.25;5.08)
country	−0.368	0.5928	.55	0.69	(0.17;2.81)
method	0.884	0.2022	<.01	2.42	(1.50;3.90)

Diagnostic odds ratio (DOR) of MUC7 for the diagnosis of BC. As shown in Figures 3 and 4 and Table 2.Based on the extracted data, we got the following diagnostic quantitative results: the pooled SEN and SPE were 0.74 (95% CI: 0.71–0.77) and 0.92 (95% CI: 0.90–0.95), and PLR and NLR were 9.58 (95% CI: 5.4–17.0) and 0.27 (95% CI: 0.20–0.36).In addition, the DOR was 40.95 (95% CI: 20.31–82.59). SROC curve for MUC7 was positioned near the desirable upper left corner, whereas area under the curve (AUC) was 0.89 (Fig. 4B). Overall, the results showed that MUC7 had a relatively high diagnostic accuracy for BC.

3.5. Threshold effect

To analyze the threshold effect, the ROC plane was plotted, and the Spearman correlation coefficient was calculated. Figure 5 displays the ROC plane, which demonstrated a nontypical "shoulder-arm" distribution. The calculated Spearman correlation coefficient was 0.196, and the corresponding *P* value was .542 ($P > .05$). This result indicates that there was no significant threshold effect present in the meta-analysis.

3.6. Meta-regression

Heterogeneity existed in the pooling data of SEN, SPE, NLR, DLR, and DOR. Therefore, meta-regression was used to detect the source of potential heterogeneity. The 12 included studies were divided into 2 Japan studies, 2 German studies and 8 China studies by region. As before, the included studies were classified as 4 Nested RT-PCR studies, 6 RT-PCR studies, 1 immunohistochemistry study and 1 Elisa studies by the test method. The included studies were separated into 1 study with the blood sample, 2 studies with tissue, and 9 studies with urine by sample type. The meta-regression was performed and the result showed that only the study method significantly accounted for the heterogeneity [Std. Err = 0.20, ratio of diagnostic odds ratio = 2.42 (95% CI, 1.50–3.9), $P < .01$].The results of meta-regression were shown in Table 3.

3.7. Subgroup analysis

To explore the sources of study heterogeneity, we conducted subgroup analyses based on test method, region, and sample type. The results of SEN, SPE, PLR, NLR, and DOR for each subgroup are presented in Table 4. Additionally, I^2 and Q tests were utilized to assess study heterogeneity.

Firstly, in the subgroup analysis of the assay, studies employing RT-PCR demonstrated superior diagnostic accuracy in terms of SEN (0.77 vs 0.62), SPE (0.95 vs 0.88), and DOR (73.65 vs 14.47) compared to studies using Nested RT-PCR. However, concerning heterogeneity, although the DOR showed low heterogeneity between the 2 groups, the other metrics (SEN, SPE, NLR, and PLR) exhibited high heterogeneity ($I^2 > 50\%$).

Next, within the study region subgroups, research conducted in China exhibited higher diagnostic efficacy in terms of SEN (0.77 vs 0.60 vs 0.68), SPE (0.99 vs 0.97 vs 0.82), and DOR (53.3 vs 42.23 vs 13.98) compared to studies conducted in Japan, Germany. Regarding the source of heterogeneity, none of the subgroups showed heterogeneity below 50% in terms of SEN, SPE, NLR, and DOR, except for PLR, which demonstrated low heterogeneity in all groups.

Finally, in the subgroup analysis based on specimen type, the diagnostic efficacy of subgroups using urine and tissue were comparable in terms of SEN (0.75 vs 0.75) and DOR (42.42 vs 43.47). However, the SPE of the urine subgroups was lower than that of the tissue subgroups (0.92 vs 0.96). Concerning the source of heterogeneity, urine subgroups displayed higher heterogeneity ($I^2 > 50\%$), while tissue subgroups exhibited lower heterogeneity ($I^2 < 50\%$).

3.8. Publication bias

Begg funnel plot test was conducted to evaluate the publication bias (Fig. 6).

Eegg value was 3.21 (95% CI: 1.31–7.69) and *P* value was .01 implied that publication bias existed in this meta-analysis.

4. Discussion

BC ranks thirteenth among the deadliest and tenth among the most common cancers worldwide.[1]It is known for its unfavorable clinical prognosis, high mortality rates, and frequent recurrence once the tumor reaches the invasive stage. Early diagnosis and prompt treatment are crucial for improving outcomes in bladder cancer patients. Currently, cystoscopy and urine cytology are the primary methods for diagnosing bladder cancer.

Cystoscopy, while effective, has drawbacks due to its invasive nature and limited sensitivity to detecting carcinoma in situ. On

Table 4

Subgroup analysis of MUC7 in the diagnosis of bladder cancer.

Subgroup	No.studies (case)	SEN			SPE			NLR			PLR			DOR		
		Value (95% CI)	I^2 (%)	*P* value	Value (95% CI)	I^2 (%)	*P* value	Value (95% CI)	I^2 (%)	*P* value	Value(95% CI)	*I*2(%)	*P* value	Value (95% CI)	I^2 (%)	*P* value
Nested RT-PCR	4 (389)	0.62 (0.68–0.75)	38.4	.20	0.88 (0.82–0.92)	74.6	.01	0.43 (0.35–0.53)	26.8	.25	6.14 (2.46–15.29)	60.1	.06	14.47 (6.05–34.6)	37.8	.19
RT-PCR	6 (597)	0.77 (0.72–0.81)	76.5	<.01	0.95 (0.92–0.97)	69.4	<.01	0.21 (0.13–0.34)	76.5	<.01	12.28 (5.88–25.65)	43.3	.12	73.65 (38.57–140.64)	5.2	.38
China	8 (857)	0.77 (0.73–0.81)	82.4	<.01	0.99 (0.91–0.97)	64.3	<.01	0.22 (0.13–0.34)	83.0	<.01	9.93 (5.87–16.80)	29.5	.19	53.30 (26.38–107.70)	37.7	.13
Japan	2 (166)	0.60 (0.50–0.70)	75.7	.04	0.97 (0.89–0.99)	27.1	.241	0.43 (0.26–0.70)	77	.04	15.75 (4.63–53.50)	0.00	.91	42.23 (11.09–160.83)	0.00	.86
German	2 (163)	0.68 (0.56–0.79)	0.0	.41	0.82 (0.73–0.89)	52.5	.15	0.38 (0.27–0.55)	14.7	.18	3.99 (2.47–6.45)	47.7	.17	13.98 (2.58–75.64)	54.2	.14
Urine	9 (1041)	0.75 (0.72–0.79)	82.1	<.01	0.92 (0.89–0.94)	76.4	<.01	0.25 (0.18–0.35)	80.8	<.01	9.37 (4.88–17.99)	71.1	<.01	42.42 (18.54–97.04)	69.8	<.01
Tissue	2 (89)	0.75 (0.63–0.85)	0.0	.84	0.96 (0.77–0.99)	0.0	.42	0.28 (0.18–0.43)	0.0	.76	11.54 (2.43–54.80)	0.0	.92	43.47 (7.05–268.00)	0.0	.87

CI = confidence interval, DOR = diagnostic odds ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio, RT-PCR = reverse transcription polymerase chain reaction, SEN = sensitivity, SPE = specificity.

the other hand, urine cytology suffers from the disadvantage of low sensitivity when it comes to identifying low-grade tumors. These limitations highlight the need for more accurate and less invasive diagnostic approaches in the field of bladder cancer detection and management.

The disadvantages of cystoscopy include its invasive nature and insensitivity to carcinoma in situ, while urine cytology's drawback lies in its low sensitivity to low-grade tumors. All of these factors significantly affect their clinical application as diagnostic and surveillance tools for bladder cancer. Thus, it is urgent to explore noninvasive and highly effective markers for BC. One of the novel promising markers, MUC7, has been investigated most frequently in recent years.

In the current systematic review and meta-analysis, twelve studies that met the inclusion and exclusion criteria, involving 1186 subjects (728 with BC and 458 without BC), were evaluated. The pooled SEN and SPE were 0.74 (95% CI: 0.71–0.77) and 0.92 (95% CI: 0.90–0.95), respectively. The pooled PLR and NLR were 9.58 (95% CI: 5.4–17.0) and 0.27 (95% CI: 0.20–0.36), respectively. The DOR and AUC were 40.95 (95% CI: 20.31–82.59) and 0.91, respectively. These results indicate that MUC7 exhibits relatively high diagnostic accuracy for BC.

The PLR of 9.58 in this study suggests that patients with BC have more than a 9-fold higher chance of testing positive for MUC7 compared to patients without BC. Conversely, the NLR of 0.27 indicates that if the MUC7 test is negative, there is up to a 27% probability that these patients still have BC. In other words, MUC7-negative results cannot be solely relied upon to exclude BC.

DOR is a single index that combines SEN and SPE to represent diagnostic accuracy. It is calculated as the ratio of the odds of positive test results in participants with the disease to the odds of positive test results in participants without the disease. DOR values range from 0 to infinity, with higher values indicating higher accuracy. In this meta-analysis, the pooled DOR of MUC7 was 40.95, signifying that MUC7 demonstrates relatively high accuracy in diagnosing BC. The SROC curve and AUC are important diagnostic indexes in meta-analysis. The position of the SROC curve is characterized in terms of the overall diagnostic odds ratio and the magnitude of inter-study heterogeneity in the odds ratio.[17] The AUC was regarded as potentially useful summaries of the curve and it ranges from 1 to 0, when the value was 1, it indicates it is a perfect test and the test can correctly classify all patients and healthy people. When the value was 0, it indicates the test is not an accurate diagnosis. In addition to the above, AUC is particularly stable when heterogeneity is tested. The AUC also shows extremely steady performance in heterogeneity tests. In our meta-analysis, the AUC of MUC7 was 0.91, indicating that MUC7 showed relatively high accuracy in the diagnosis of BC.

Heterogeneity is a potential factor affecting the results of the meta-analysis. By the heterogeneity test, it was found that there was also high heterogeneity in this meta-analysis. Through the ROC plane distribution and Spearman correlation analysis, we know that the threshold effect is not the source of heterogeneity. To further explore the source of heterogeneity, meta-regression and subgroup analysis were performed. The results of meta-regression show that the different experimental methods may be the source of heterogeneity. Subgroup analysis showed that the heterogeneity of each subgroup did not decrease significantly at the same time, this means that we have not found the source of heterogeneity. There may be other factors influencing the sources of study heterogeneity, such as the design of PCR primers. Different primers used in PCR amplification may have varying efficiencies. However, each study designed its own primers, and in some cases, the primer sequences were not publicly available, making it impossible to assess primer design heterogeneity. The gold standard for disease diagnosis can also be a source of heterogeneity. In our included studies, the diagnosis of bladder

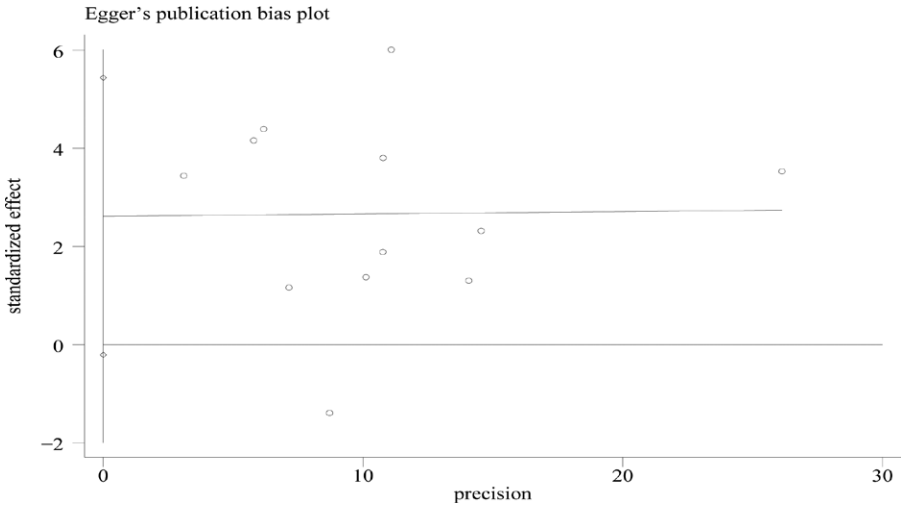

Figure 6. Begg funnel plot for publication bias.

cancer mainly relied on pathological examination. However, the reagents used in pathological diagnosis and the expertise of pathologists varied among studies, leading to differences in the ability to diagnose bladder cancer. This source of heterogeneity may remain unmeasurable. Some studies designs and the use of blinding methods could also contribute to heterogeneity. However, all the studies included in this analysis were case-control studies, which eliminates heterogeneity arising from different study designs. Additionally, all the studies employed blinding methods, making blinding not a source of heterogeneity.

Begg funnel plot test was conducted to evaluate the publication bias, and significant bias was observed in the current study. Publication bias might be related to language selection, or it might be related to the difficulty of publishing negative studies. In conclusion, heterogeneity exists among the subgroups included in the study, and we cannot further analyze the source of heterogeneity. Therefore, it is necessary to include more research in our research.

In addition to consistency, this study still has several limitations. First of all, Although the search scope is wide and the search strategy is scientific, but the languages were limited to Chinese and English and many gray documents such as supplements, administrative records and meeting minutes were difficult to obtain, this might lead to publication bias. Secondly, most of the included literature was retrospective studies design, which might restrict our ability to access the accuracy of MUC7 due to patient selection bias. In the end, The sample size of the included literature is relatively small, with a total of 728 BC patients and 458 controls investigated in all 12 studies.

5. Conclusion

The meta-analysis showed that MUC7 showed high sensitivity and specificity in the diagnosis of bladder cancer. Therefore, it may become a new noninvasive new diagnostic method for bladder cancer. More prospective studies with large sample size and multicenter design are necessary to get more evidence on the value of MUC7 in BC diagnosis.

Author contributions

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