Urologia Internationalis

Systematic Review

Urol Int 2025;109:399–411
DOI: 10.1159/000546014

Received: January 14, 2025
Accepted: April 14, 2025
Published online: May 2, 2025

The Value of Circulating Tumor DNA in the Prognostic Diagnosis of Bladder Cancer: A Systematic Review and Meta-Analysis

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Keywords
Circulating tumor DNA · Bladder cancer · Prognostic assessment · Meta-analysis · Biomarker

Abstract
Introduction: Circulating tumor DNA (ctDNA) is a noninvasive liquid biopsy technique that can reflect the dynamic changes of tumors in real time. This study aims to clarify the predictive value of ctDNA detection for disease progression and metastasis risk in bladder cancer patients through systematic review and meta-analysis, providing a scientific basis for clinicians' individualized treatment decisions and risk stratification management for patients. ***Methods:*** Studies related to ctDNA in prognostic assessment of bladder cancer were screened by systematically searching PubMed, Cochrane Library, Web of Science, Willey library, CNKI, and other databases, and the search was from inception to December 2024, and the data were extracted and analyzed by Meta-analysis. ***Results:*** A total of 9 papers were included, and the results showed that ctDNA testing had a sensitivity of 0.68 (95% CI: 0.54–0.78), specificity of 0.76 (95% CI: 0.51–0.90), and an area under the curve of 0.75 (95% CI: 0.71–0.79), suggesting that it has a moderate level of diagnostic efficacy in the assessment of prognosis in bladder cancer. Positive likelihood ratio and negative likelihood ratio were 2.8 (95% CI: 1.24–6.35) and 0.43 (95% CI: 0.28–0.65), respectively, with a diagnostic odds ratio of 6.56 (95% CI: 2.12–20.33). Fagan's nomogram analysis showed that when the prior probability was 50%, the posttest probability increased to 74% for positive results and decreased to 30% for negative results. Deeks' funnel plot analysis indicated no significant publication bias (p = 0.24). A high level of heterogeneity (I^2 > 80%) was observed among the studies, which may stem from differences in detection techniques, disease stages of patients, and follow-up periods. Publication bias analysis revealed no significant bias (p = 0.24). ***Conclusion:*** ctDNA demonstrates some clinical application value in the prognostic assessment of bladder cancer and can assist in predicting patient recurrence and survival. However, its independent predictive efficacy is not enough to replace traditional assessment methods. Future studies should aim to optimize the detection technology, unify the study design, expand the sample size, and combine multi-omics data for joint analysis, in order to further improve its potential application in the prognostic assessment of bladder cancer.

Introduction

Bladder cancer is one of the most common malignant tumors of the urinary tract with a high incidence worldwide, especially in industrialized countries [1, 2].

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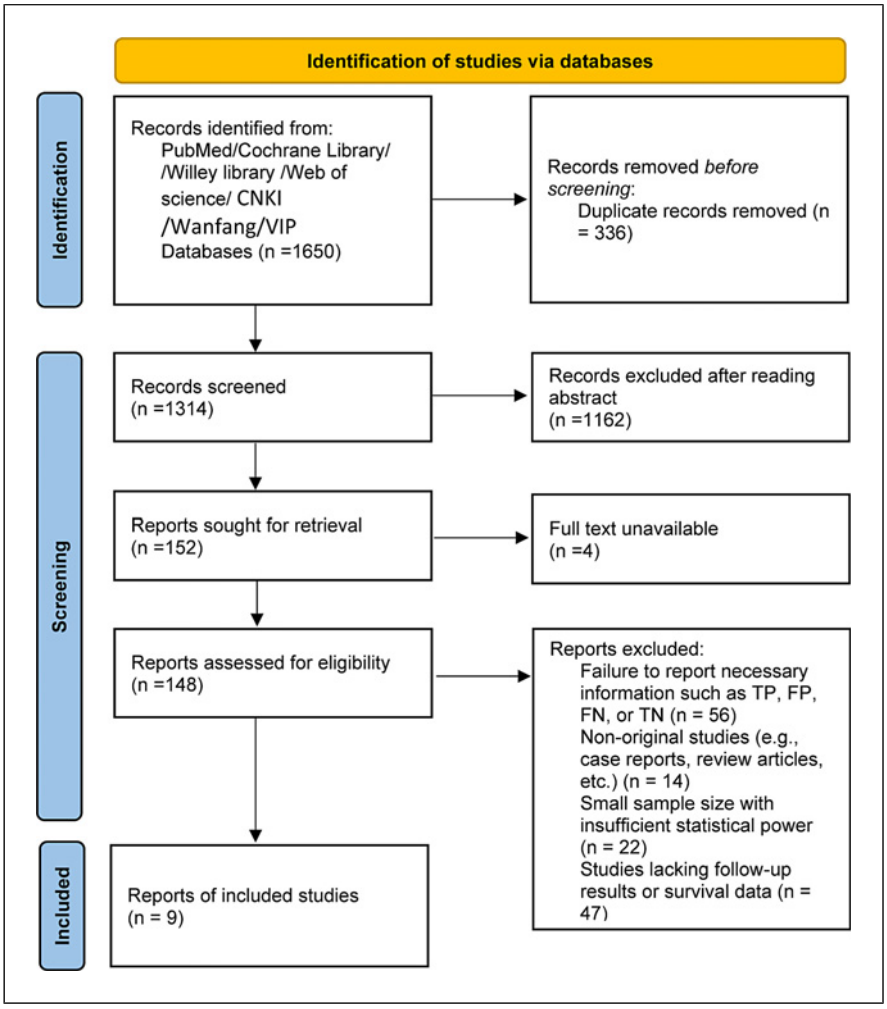

Fig. 1. Schematic diagram of the literature screening process.

According to global cancer statistics, bladder cancer accounts for more than 500,000 new cases and 200,000 deaths annually [3]. Bladder cancer is mainly classified into non-muscle-invasive bladder cancer and muscle-invasive bladder cancer, which have significant differences in biological behaviors, treatments and prognosis [4]. Although surgical procedures such as transurethral resection of bladder tumor [5] and radical cystectomy [6] combined with adjuvant therapy have significantly improved the overall survival rate of patients, the high recurrence rate and the risk of progression of bladder cancer remain the prognostic of bladder cancer. Clinically, the diagnosis and surveillance of bladder cancer mainly rely on imaging, cystoscopy and urine cytology [7]; however, these traditional methods have many limitations, such as the invasiveness of cystoscopy, the difficulty of detecting microscopic lesions by imaging, and the insufficient sensitivity (SEN) of urine cytology [8, 9]. In recent years, liquid biopsy, as an emerging noninvasive detection technique, has demonstrated significant value in the early diagnosis, monitoring of recurrence, and evaluation of treatment response in a variety of cancers [10]. Among them, circulating tumor DNA (ctDNA), as an important component of liquid biopsy, has become a hotspot of research because of its ability to reflect tumor dynamics in real time and capture tumor-specific mutations and genomic features [11–13].

ctDNA is a DNA fragment released into the peripheral blood by tumor cells through necrosis, apoptosis, or active secretion. ctDNA has unique tumor-specific genetic alterations, such as mutations, copy number variations, and methylation abnormalities, compared with normal cellular DNA [14]. In bladder cancer, common ctDNA-associated mutations include TERT promoter mutations, TP53 mutations,

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Table 1. General information on the included literature

Author	Year	Country/ region	Study type	Sample size		Sex ratio		Age		Detection methods	ctDNA concentration	
				experimental group	control group	experimental group	control group	experimental group	control group		experimental group	control group
Carrasco et al. [16]	2022	Spain	Retrospective study	39	31/8		51–85	NGS	–	–		
Carrasco et al. [17]	2023	Spain	Prospective study	10	32	9/1	30/2	69	66	droplet digital PCR	–	–
Gazzaniga et al. [18]	2012	Italy	Case-control	20	24	38/6		51–78	51–78	RT-PCR	1–3 ng/mL	1–3 ng/mL
Haga et al. [19]	2020	Japan	Case-control	13	13	12/1	12/1	69±11	75±10	RT-PCR	4.8±3.1 ng/mL	2.6±2.4 ng/mL
Sfakianos et al. [20]	2024	USA	Retrospective study	167	124/43		33–89	33–89	NGS	–	–	
Yang et al. [21]	2021	China	Retrospective study	153	43	–	–	>18	>18	RT-PCR	–	–
Zhang et al. [12]	2021	China	Retrospective study	43	39	13/69		32–83	droplet digital PCR	404–3,965 copies	404–3,965 copies	
Wu et al. [22]	2024	China	Case-control	50	18	30/20	10/8	56.32±6.32	58.23±6.22	RT-PCR	12.19±8.25 ng/mL	16.23±8.65 ng/mL
Yang et al. [23]	2022	China	Case-control	46	50	29/17	31/19	58.4+2.2	55.1±2.9	RT-PCR	–	–

Table 2. NOS quality scores of included studies

Study ID	Selection of study subjects (4 points)	Comparability of groups (2 points)	Outcome assessment (3 points)	Total score (9 points)
Carrasco et al. [16]	4	2	1	7
Carrasco et al. [17]	4	1	2	7
Gazzaniga et al. [18]	3	2	2	7
Haga et al. [19]	3	2	1	6
Sfakianos et al. [20]	4	1	1	6
Yang et al. [21]	4	1	2	7
Zhang et al. [12]	3	2	2	7
Wu et al. [22]	3	2	1	6
Yang et al. [23]	3	1	2	6

and FGFR3 mutations, which not only serve as diagnostic markers for tumors, but also are closely associated with disease progression, recurrence, and treatment response [15]. In addition, ctDNA testing is noninvasive, highly sensitive, and reproducible, especially showing great potential in monitoring bladder cancer recurrence and predicting treatment efficacy [16]. Although many studies have been conducted to investigate the value of ctDNA in bladder cancer, its accuracy and reliability in prognostic diagnosis are still controversial [16–18]. On the one hand, differences in detection techniques (e.g., digital PCR and next-generation sequencing technology), marker selection, and patient characteristics among different studies may lead to inconsistent results. On the other hand, a comprehensive evaluation of ctDNA in the prognostic diagnosis of bladder cancer is lacking. Therefore, it is necessary to integrate the existing research evidence through systematic evaluation and meta-analysis to comprehensively assess the SEN and specificity (SPE) of ctDNA in the prognostic diagnosis of bladder cancer and its clinical application value.

The aim of this study was to systematically evaluate the diagnostic efficacy of ctDNA in the assessment of metastasis and risk of disease progression in bladder cancer patients. By analyzing the diagnostic performance of different assays and markers, we hope to provide more reliable evidence to support the application of ctDNA in the clinical diagnosis and treatment of bladder cancer, and at the same time, make constructive suggestions for future research directions and clinical practice.

Methods

Study Design

This study adopts the method of systematic evaluation and Meta-analysis, aiming to comprehensively assess the diagnostic performance of ctDNA in the prognostic diagnosis of bladder cancer. In order to ensure the rigor and reliability of the study, this study was conducted in strict compliance with the specifications of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We will include prospective or retrospective studies that meet specific criteria for evaluating key diagnostic indicators such as SEN, SPE, positive predictive value (PPV), negative predictive value (NPV), and other key diagnostic indicators of ctDNA in the prognostic diagnosis of bladder cancer, aiming to comprehensively assess the value of ctDNA as a liquid biopsy tool for metastatic diagnosis. The protocol for this systematic review was registered with PROSPERO (number: CRD42025640672).

Literature Search

To ensure the comprehensiveness and accuracy of the study, an extensive literature search was carried out in several authoritative databases, including PubMed, Web of science, Cochrane Library, Wiley Library, as well as the Chinese databases CNKI, Wanfang, and Wipro (VIP) databases. The following keywords were used during the search: "circulating tumor DNA," "ctDNA," "bladder cancer," "metastasis," "sensitivity," "specificity," etc., and keyword combinations were performed by Boolean logic operators (e.g., AND, OR) to ensure that as much relevant

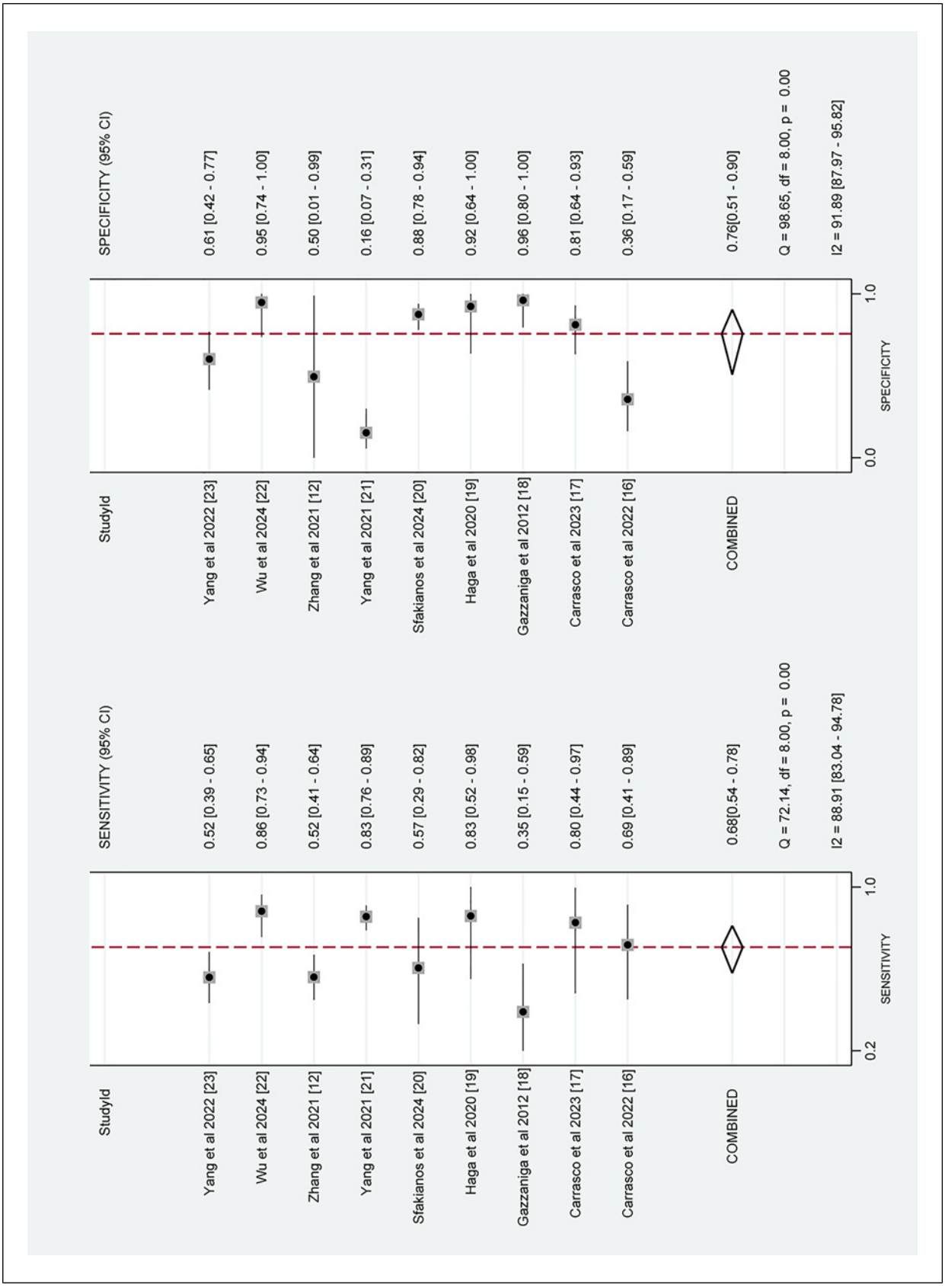

Fig. 2. SEN and SPE of ctDNA in bladder cancer prognosis.

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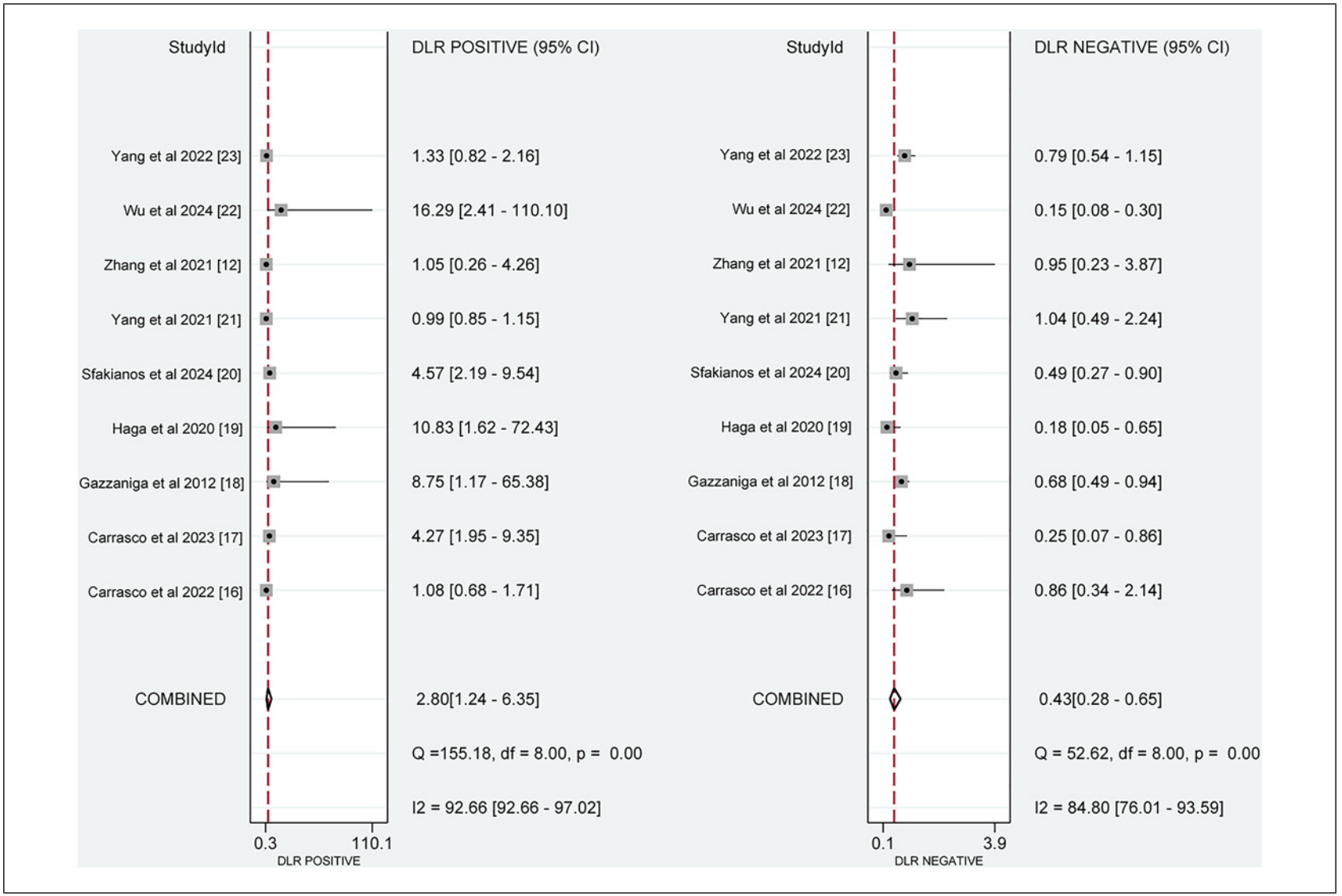

Fig. 3. PLR and NLR of ctDNA in prognostic diagnosis of bladder cancer.

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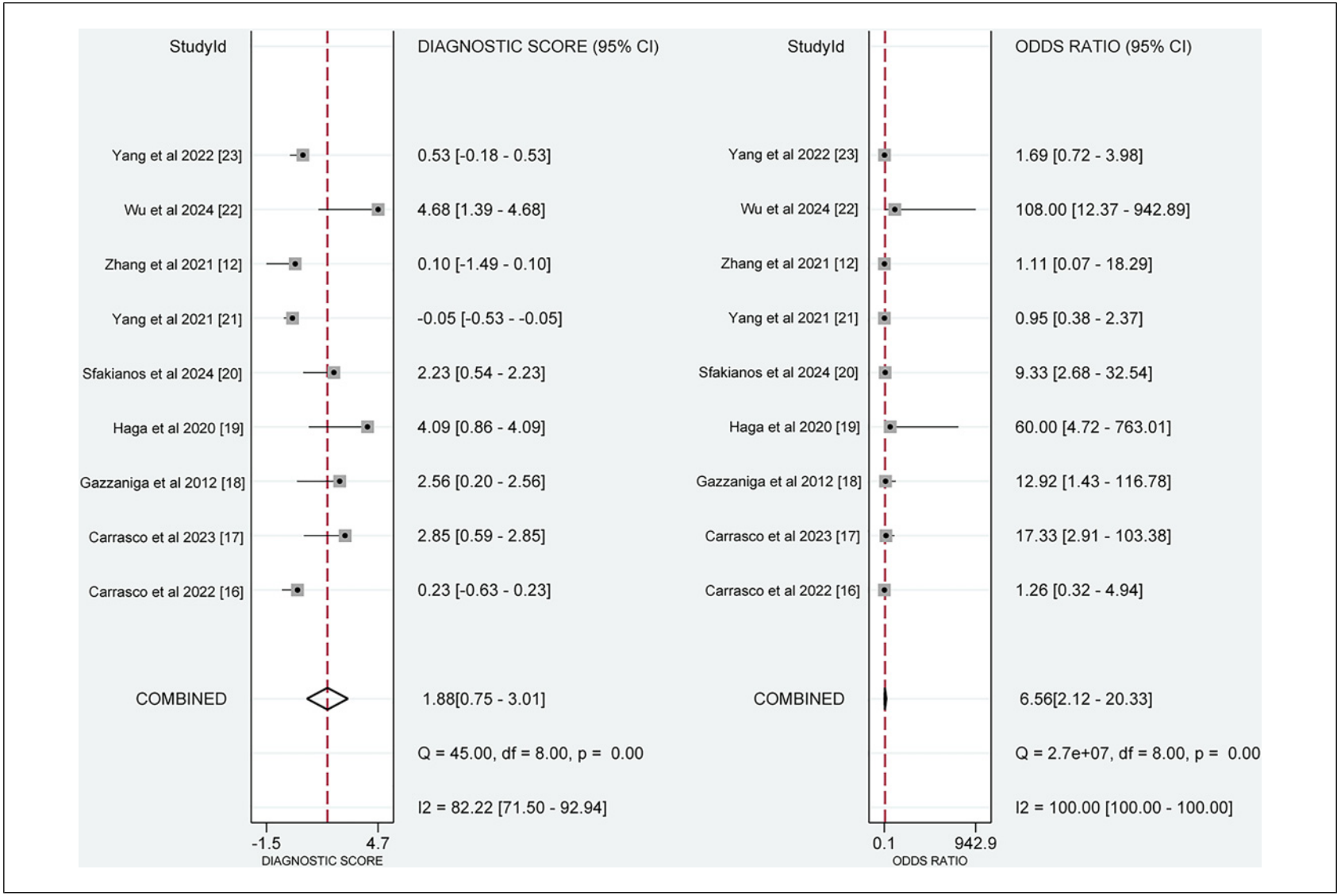

Fig. 4. Diagnostic score and DOR of ctDNA in the prognostic diagnosis of bladder cancer.

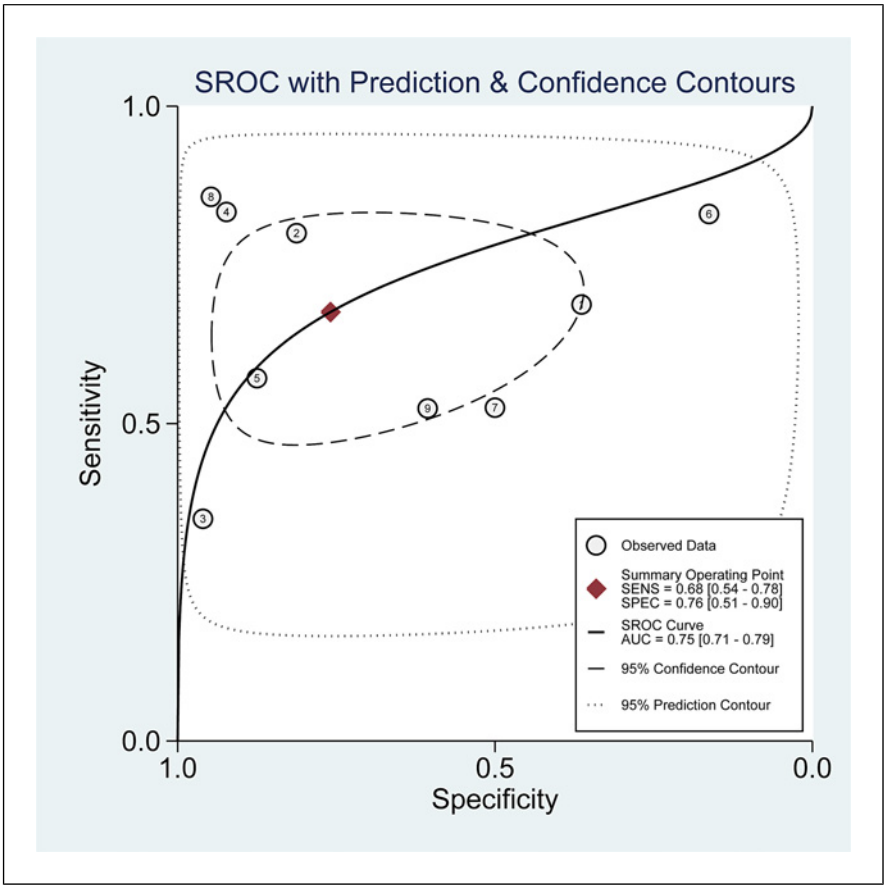

Fig. 5. SROC of ctDNA in the diagnosis of bladder cancer metastasis.

literature as possible was covered. Meanwhile, in order to improve the accuracy and comprehensiveness of the search, relevant MeSH terms (e.g., "Bladder Cancer," "Metastasis," "Circulating Tumor DNA") for advanced search, the search period was from inception to December 2024. This study was prepared according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and completed 27-point checklist PRISMA.

Literature screening strictly adhered to the inclusion and exclusion criteria defined by the PICO framework to ensure transparency and reproducibility in the study selection process. The PICO framework for this study is as follows:

1. Population (P): patients with pathologically confirmed bladder cancer;
2. Intervention (I): ctDNA detection;
3. Comparison (C): traditional clinical follow-up methods (e.g., imaging, pathological diagnosis, or cystoscopy);
4. Outcome (O): predictive efficacy for bladder cancer progression or metastasis risk, with at least SEN, SPE, PPV, and NPV provided.

Additionally, included studies must provide sufficiently detailed statistical data (true positives, false positives, true negatives, and false negatives) to meet the requirements for meta-analysis. The exclusion criteria then included the following: (1) the study subjects were not bladder cancer patients, or the study topics were not directly related to bladder cancer; (2) studies that lacked data related to ctDNA testing; and (3) studies with poor quality study design or insufficient data to support Meta-analysis. Literature screening and data extraction were done by two independent investigators to minimize the risk of selection bias. For disagreements that arose during the screening process, agreement was reached through discussion and negotiation, and third-party experts were invited to review and arbitrate when necessary to ensure the scientific validity and consistency of the included literature.

Data Extraction and Quality Assessment

After literature screening and inclusion, this study conducted systematic data extraction for all studies that met the inclusion criteria. First, basic information about the studies was extracted, including authors, year of

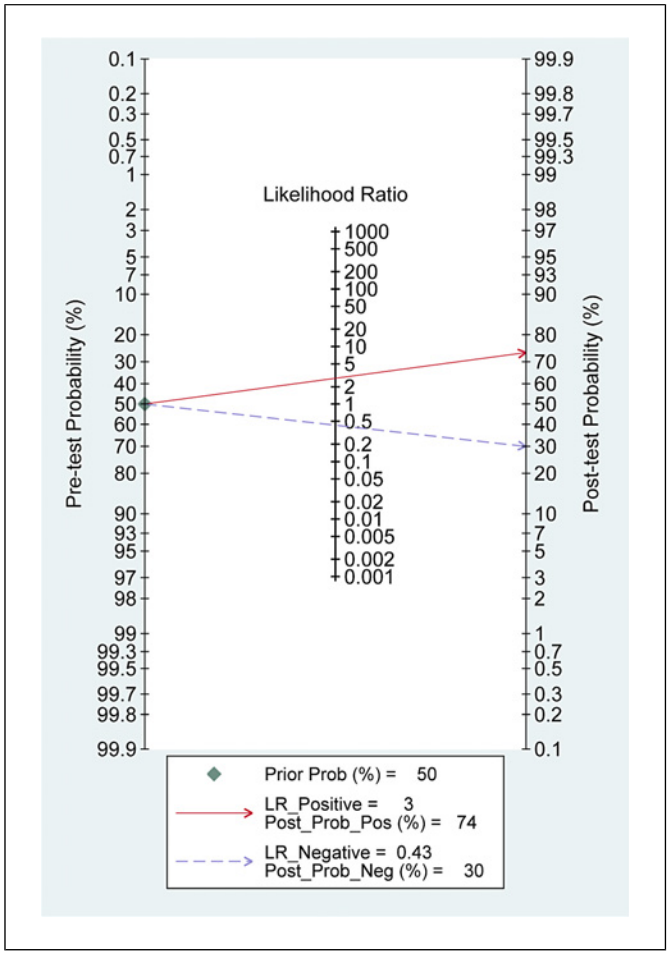

Fig. 6. Fagan plot of ctDNA in the prognostic diagnosis of bladder cancer.

publication, sample size, study design (e.g., prospective or retrospective study), and geographic area covered by the study, as well as diagnostic performance indicators, including SEN, SPE, PPV, and NPV. In addition, to ensure the reliability and scientific validity of the quality of the included studies, the Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included literature. The NOS scale scores the quality of the literature in terms of the selectivity of the studies, comparability, and assessment of the exposure or outcome. Based on the scoring results, the risk of bias of the studies was further determined to provide reliable basic data support for the subsequent meta-analysis.

Statistical Analysis

In this study, data from the included literature were statistically analyzed using Stata 13.0 software to comprehensively assess the clinical value of ctDNA in the diagnosis of bladder cancer metastasis. First, the diagnostic efficacy indexes of each study were combined through a bivariate random-effects model, including SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). Meanwhile, summary receiver operating characteristic (SROC) curves were plotted and the area under the curve (AUC) was calculated to assess the overall diagnostic performance of ctDNA in the diagnosis of bladder cancer metastasis. Second, in order to explore the heterogeneity among the included studies, Cochran's Q test and I^2 statistic were used to assess the heterogeneity, where $I^2 > 50\%$ indicated significant heterogeneity. Finally, potential publication bias was assessed by Deeks' funnel plot asymmetry test, and the results were visualized using funnel plots, and a priori and posteriori probabilities were assessed by Fagan plots, and all the statistical results were considered statistically different by the bivariate test of $p < 0.05$.

Results

Literature Search to Include Basic Characteristics of the Literature

A total of 1,650 literature related to the research topic were retrieved through systematic search. After removing 336 duplicates, the remaining 1,314 documents entered the title and abstract screening stage. After the initial screening, 1,162 literature that did not meet the inclusion criteria were excluded, and the remaining 152 literature entered the full-text access stage, of which 4 literature were excluded because they could not be accessed in full text. After full-text assessment of 148 literature, 139 literature were further excluded for the following reasons: 56 did not report key data (e.g., TP, FP, FN, or TN), 14 were non-original studies such as case reports or reviews, 22 had insufficient sample sizes (low statistical efficacy), and 47 lacked follow-up results or survival data. Ultimately, nine papers were included that met the study criteria and were used in the meta-analysis. The specific screening process is shown in Figure 1, and details of the included literature are shown in Table 1.

Quality Evaluation of Included Literature

This study evaluated the quality of the nine included literature using NOS, which was scored mainly in terms of the selectivity of the study population, comparability between groups, and the method of measuring the outcomes. The results showed that the NOS scores of all the included studies were 6 and above, indicating that the overall study quality was high (Table 2).

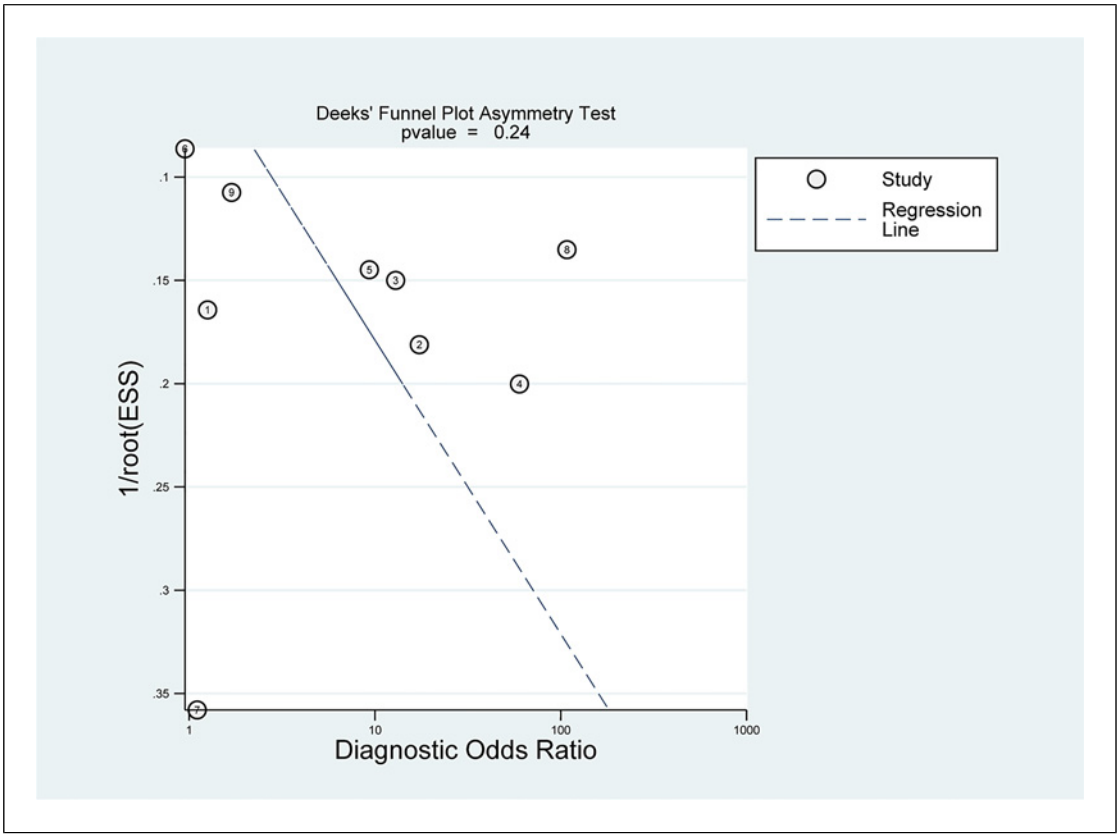

Fig. 7. Deeks funnel plot to assess publication bias.

Meta-Analysis Results

Diagnostic Efficacy Analysis of Ultrasound Features

A total of 9 papers were included in this meta-analysis to assess the combined efficacy of ctDNA in the diagnosis of bladder cancer metastasis. Comprehensive calculations showed that the SEN of ctDNA was 0.68 (95% CI: 0.54–0.78), I^2 = 88.91%, and the SPE was 0.76 (95% CI: 0.51–0.90), I^2 = 91.89%, as shown in Figure 2. The results suggest that ctDNA has a moderate level of SEN and SPE in metastasis diagnosis, but with a high degree of heterogeneity. Further analysis showed a PLR of 2.80 (95% CI: 1.24–6.35), I^2 = 92.66%, indicating that ctDNA at the time of a positive test increases the likelihood of a diagnosis of bladder cancer metastasis but is not sufficient to fully confirm the diagnosis. The NLR was 0.43 (95% CI: 0.28–0.65), I^2 = 84.80%, indicating that the possibility of metastasis could still not be completely excluded when the test was negative, as shown in Figure 3. Diagnostic Score was 1.88 (95% CI: 0.75–3.01), I^2 = 82.22%, while DOR was 6.56 (95% CI: 2.12–20.33), I^2 = 100.00%, as shown in Figure 4, suggesting that the combined diagnostic value was more limited. By plotting the SROC curve and calculating the AUC, the results showed that the AUC was 0.75 (95% CI: 0.71–0.79), indicating that ctDNA had a certain diagnostic efficacy in the diagnosis of bladder cancer metastasis, as shown in Figure 5. However, the AUC value and the high heterogeneity both indicated that the diagnostic performance was greatly influenced by factors such as study quality, sample characteristics, and detection methods.

A Priori Probability and Posterior Probability

In this study, we assessed the impact of ctDNA testing on the a posteriori probability of prognostic diagnosis of bladder cancer at different a priori probabilities by Fagan plot analysis. The results showed that with an a priori probability of 50%, a PLR of 2.8 increased the a posteriori probability of a positive test result to 74%, while an NLR of 0.43 decreased the a posteriori probability of a negative test result to 30%. This result suggests that ctDNA testing has some clinical application in the diagnosis of bladder cancer metastasis and can significantly affect the a posteriori probability of diagnosis in different clinical settings, as shown in Figure 6.

Publication Bias

In this study, publication bias of the included studies was assessed by Deeks funnel plot. The results showed that the slope of the funnel plot regression line was close to zero with a p value of 0.24 ($p > 0.05$), indicating that there was no significant publication bias in the included studies. This shows that the combined results of diagnostic efficacy are highly robust, as shown in Figure 7.

Discussion

This study systematically reviewed and meta-analyzed the diagnostic efficacy of ctDNA in the prognostic evaluation of bladder cancer. The results indicate that ctDNA testing has potential utility in assessing disease progression and metastasis risk in bladder cancer patients. The pooled analysis revealed a SEN of 0.68, a SPE of 0.76, and an AUC value of 0.75, suggesting that ctDNA demonstrates moderate predictive capability for disease progression and metastasis in bladder cancer patients. However, the heterogeneity analysis showed high I^2 values, indicating significant heterogeneity among the included studies, which may be closely related to the differences in Study Design, patient population characteristics, detection techniques and follow-up time.

In bladder cancer patients, ctDNA content and its specific molecular features (e.g., mutations, methylation, copy number variation, and fragmentation patterns) can reflect tumor load, invasiveness, and metastatic potential [24, 25]. Studies have shown that mutations in specific genes (e.g., TP53, FGFR3, PIK3CA, etc.) or aberrant detection of methylation markers in ctDNA are highly tumor-specific, and these features are closely associated with disease progression and patient survival in bladder cancer [26]. For example, elevated ctDNA levels may indicate the presence of residual lesions or micrometastatic lesions, which in turn lead to an increased risk of recurrence [20]. In addition, ctDNA changes can dynamically monitor therapeutic response and drug resistance mechanisms, such as detecting changes in the mutation frequency of tumor-related genes during immunotherapy or chemotherapy, to support therapeutic decisions [12]. Therefore, the significant role of ctDNA testing in the prognosis management of bladder cancer lies in its ability to provide real-time molecular evidence of tumor biological characteristics and disease progression risk, assisting clinicians in more accurately assessing the risk of disease progression and metastasis in patients.

Further analysis of the results of this study revealed that the PLR for ctDNA detection was 2.8, and the NLR was 0.43. This indicates that a positive ctDNA result significantly increases the risk of disease progression or metastasis in patients, while a negative ctDNA result, although suggesting a relatively lower risk of disease progression, cannot completely rule out the possibility of further disease development. Additionally, Fagan's nomogram analysis showed that in a clinical scenario with a prior probability of 50%, a positive ctDNA result increased the actual probability of disease progression or metastasis from 50% to 74%, whereas a negative result reduced it to 30%. These findings demonstrate that ctDNA testing has practical clinical significance in the risk stratification and management of bladder cancer patients, particularly when combined with traditional clinical indicators, significantly enhancing the precision of clinical decision-making.

Although the results of this study suggest the diagnostic and predictive value of ctDNA, there are some limitations. First, the high heterogeneity among the included studies (all I^2 values >80%) may have been influenced by (1) differences in assay technology, such as differences in SEN and SPE of different platforms, which may affect the accuracy of the results; (2) differences in patient characteristics, including differences in tumor stage, pathology type, and treatment regimens; and (3) inconsistencies in the study design and duration of follow-up may have led to endpoint event definition differences. Second, the small sample sizes of some studies may have affected statistical efficacy, thus limiting the robustness of the results. Finally, due to incomplete data, this study failed to analyze in depth the predictive role of specific molecular features in ctDNA (e.g., specific gene mutations or methylation patterns) on the prognosis of bladder cancer, which may limit the depth of the mechanistic explanation.

Future research should focus on the following aspects to better advance the application of ctDNA in the clinical prognosis assessment of bladder cancer.

1. Conduct large-scale, multicenter, standardized prospective studies to reduce research heterogeneity and enhance the clinical value of ctDNA detection in predicting disease progression and metastasis risk.
2. Conduct in-depth analyses of the specific impact of different molecular characteristics on the prognosis of bladder cancer patients, clarifying the molecular mechanisms linking ctDNA detection to disease progression.
3. Develop comprehensive risk models that integrate ctDNA with traditional clinical assessment indicators,

promoting the further integration of ctDNA testing into clinical practice to achieve precise risk assessment and treatment decision support for patients.

Conclusion

In summary, ctDNA shows some potential for clinical application in the prognostic assessment of bladder cancer. By reflecting the biological characteristics and dynamic changes of tumors, ctDNA can provide a molecular-level basis for recurrence and survival prediction of bladder cancer patients. However, due to the heterogeneity of studies and technical limitations, its independent predictive value is not enough to replace traditional clinical indicators. In the future, the detection technology should be further optimized, the sample size should be expanded, and multidimensional integrated analysis should be explored to promote the clinical translational application of ctDNA in the prognostic assessment of bladder cancer.

Statement of Ethics

A Statement of Ethics is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study is supported by the Jiaxing Science and Technology Plan (No. 2025CGW050).

Author Contributions

Conception and design: Yu Lu, Huajun Wu, Jian Jiang, and Siwen Bao. Acquisition of data: Yu Lu, Huajun Wu, Jian Jiang, Siwen Bao, and Chen Ling. Collection and assembly of data: Yu Lu, Huajun Wu, Jian Jiang, Siwen Bao, and Chen Ling. Data analysis and interpretation: Chen Ling. Manuscript writing: Yu Lu, Huajun Wu, Jian Jiang, Siwen Bao, and Chen Ling. Final approval of manuscript: Yu Lu, Huajun Wu, Jian Jiang, Siwen Bao, and Chen Ling.

Data Availability Statement

The data used to support the findings of this study are included within the article. Further inquiries can be directed to the corresponding author.

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