The Diagnostic Value of LncRNAs for Bladder Cancer: A Meta-Analysis

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Abstract

Background: In recent years, qualitative and quantitative analysis of LncRNA has been reported as a potential method for early diagnosis of bladder cancer, but the results from each research are insufficient and not completely consistent. This meta-analysis aims to evaluate the diagnostic value of LncRNA for BC.

Methods: We conducted a diagnostic meta-analysis and the diagnostic significance of LncRNA in blood, urine and tumor tissues was discussed. We searched the PUBMED, EMABASE, and Cochrane Library until June 2020. The current meta-analysis was performed using Review Manager 5.2, Stata 16.0 and Meta-Disc 1.4 software.

Results: A total of 18 researches involving early and/or advanced bladder cancer were finally included. The overall diagnostic accuracy was measured as follows: pooled sensitivity and specificity were 0.72 (95%CI:0.70, 0.73) and 0.76 (95%CI: 0.75, 0.78). Pooled positive likelihood ratio and negative likelihood ratio were 3.09 (95%CI: 2.66, 3.58) and 0.37 (95%CI: 0.33, 0.42). Combined diagnostic odds ratio was 9.43 (95%CI: 7.30, 12.20). A high diagnostic accuracy was demonstrated by the summary receiver operating characteristic curve, with area under the curve of 0.82 (95%CI: 0.78, 0.85). UCA1 and H19 had the best diagnostic effect, their diagnostic sensitivity and specificity were 80%, 79% and 79%, 73% respectively, the combined diagnostic odds ratio was 16.85 and 12.67 respectively.

Conclusions: This meta-analysis suggests that LncRNA have great potential in the diagnosis of bladder cancer, UCA1 and H19 had the best diagnostic effect. LncRNA panel is the future development direction in the diagnosis of bladder cancer. However, larger sample researches are needed to further confirm our conclusion.

1. Background

Bladder cancer (BC) is the tenth most common tumor in the world, and the most common tumor in urinary system. In recent years, the incidence rate is increasing[1]. Smoking is the most important independent risk factor[2]. According to the global cancer statistics − 2020, there were 573278 new bladder cancer cases and 212536 deaths in 2018. It accounts for 4.4% of the cancer incidence rate in men and 2.9%[3] in cancer mortality. About 75% of them are non-muscle invasive bladder cancer (NMIBC)[4]. The 5-year survival rate after radical resection is 67.7%[5], but the 5-year recurrence rate after surgical resection is also as high as 70%[6]. Moreover, the recurrence cases will appear the phenomenon of deepening of malignancy, deepening of drug resistance and significantly decreasing survival rate, which is the main cause of metastasis and death of bladder cancer patients. Although, endoscopic surgery, open surgery, local or systemic immunotherapy, radiotherapy and chemotherapy are mainly used for the treatment of bladder cancer, but recurrence and chemotherapy resistance after resection of bladder cancer have become the main obstacles, thus restricting the treatment of this disease[7].

Cystoscopy has always been considered as the gold standard for the diagnosis of bladder cancer[8]. Bladder cancer monitoring also relies on repeated cystoscopy and biopsy. However, this process is very time-consuming and expensive. Sometimes it is not sensitive to carcinoma in situ[9], and may bring a series of complications, such as urinary tract injury, urinary tract infection, bladder injury, etc.[10, 11]. It may even lead to anxiety and depression before or after the cystoscopy in patients[12], which increases the pain of patients, reduces the compliance of patients' monitoring, and reduces the survival rate of patients in disguised form[13]. And even increasing the frequency of cystoscopy can't delay the disease progression and death of patients[14]. At present, there are also some non-invasive methods for the diagnosis of bladder cancer, such as urine exfoliation cytology, but it also has obvious shortcomings, its sensitivity is low[15], especially in the early stage of tumor, cell adhesion is good, it is not easy to fall off, resulting in its sensitivity is greatly reduced, in addition, inflammation, radiotherapy, chemotherapy and other may lead to false negative. Therefore, a noninvasive, simple, sensitive and specific diagnostic method for bladder cancer is urgently needed.

With the development of second-generation sequencing technology, an increased number of long noncoding RNAs (LncRNAs) have been found to be associated with urologic malignancies[16, 17]. LncRNAs are defined as non-protein coding RNAs with the length of more than 200 nucleotides. Recent researches have shown that LncRNA are closely associated with diverse biological processes, especially in various types of cancer and play an indispensable role in the metastasis and prognosis of cancer. In bladder cancer, A variety of LncRNAs have been found to play an important role in the proliferation, invasion, lymphatic metastasis and drug resistance of bladder cancer[18–21]. In addition, bladder cancer cells with abnormal expression of LncRNA often shed from tumor tissue, and apoptotic bladder cancer cells also release LncRNA into blood and urine. Therefore, the use of free LncRNA in blood and urine can be used as a noninvasive detection method. Thus, the purpose of this meta-analysis was to investigate the diagnostic value of LncRNA in bladder cancer.

2. Methods

2.1 Literature search

The publication search was performed via several databases by two authors, including Pubmed, Embace and Cochrane Library for the researches of LncRNA and bladder cancer. The publication dates used in the meta-analysis were chosen from 2006 to 2020. The search was performed by both text word and MeSH terms to increase the sensitivity. The following search terms applied in Pubmed, embace and Cochrane Library database included:(Urinary Bladder Neoplasms[MeSH] OR (Tumors, Bladder) OR (Cancer of the Bladder) OR (Urinary Bladder Cancer) OR (Bladder Tumors) OR (Bladder Cancer) OR (Cancer, Bladder) OR (Malignant Tumor of Urinary Bladder) OR (Cancer, Urinary Bladder) OR (Neoplasm, Bladder) OR (Urinary Bladder Neoplasm) OR (Neoplasms, Bladder) OR (Bladder Neoplasms) OR (Bladder Neoplasm) OR (Bladder Tumor) OR (Tumor, Bladder) OR (Bladder Cancers) OR (Neoplasm, Urinary Bladder) OR (Cancer of Bladder))AND ((RNA, Long Noncoding[MeSH]) OR (LincRNAs) OR (RNA, Long Non-Protein-Coding) OR (Noncoding RNA, Long) OR (LncRNA) OR (Long Intergenic Non-Protein Coding RNA) OR (Long Noncoding RNA) OR (Long ncRNA) OR (ncRNA, Long) OR (Long Non Protein Coding RNA) OR (Long Non-Protein-Coding RNA) OR (Long Non-Translated RNA) OR (Untranslated RNA, Long) OR (Non-Translated RNA, Long) OR (RNA, Long Non Translated) OR (Long Non-Coding RNA) OR (Long Non Coding RNA) OR (Non-Coding RNA, Long) OR (ncRNAs, Long) OR (RNA, Long Non-Coding) OR (RNA, Long Untranslated) OR (Non-Protein-Coding RNA, Long) OR (RNA, Long Non-Translated) OR (Long Intergenic Non Protein Coding RNA) OR (Long ncRNAs) OR (Long Untranslated RNA) OR (LINC RNA)) AND ("Sensitivity and specificity"[MeSH] OR diagnos*[tw] OR predict*[tw] OR accura*[tw])NOT (review OR letter OR editorial OR ‘proceeding paper’ OR “poster presentation” OR “animal experiment” OR “meta-analysis” OR “meeting abstract” OR “case report”). Moreover, the references in the available papers were also reviewed manually to obtain additional researches which met the inclusion criteria. Similarly, references of all articles in these eligible researches were also read to identify additional relevant literature.

2.2 Inclusion and exclusion criteria of the researches

Researches selected for the meta-analysis met the following inclusive criteria:

(1) Evaluation of the relationship between LncRNA expression and diagnosis of patients in human bladder cancer.

(2) All the patients were diagnosed with bladder cancer based on gold standard diagnostic test, and all patients were more than 18 years old.

(3) The true-positive, false-positive, false-negative and true-negative values can be calculated directly or indirectly.

(4) No less than 20 patients were included in all researches.

Researches that met the following exclusion criteria were removed from the meta-analysis:

(1) Data required could not be extracted directly or indirectly.

(2) For the same or similar researches of the same author, the older researches were excluded.

(3) Researches with sample size less than 20.

2.3 Data collection and quality evaluation

Two reviewers independently read the title, abstract and full text of the literature. Bias risk of data extraction and evaluation included in the researches was cross-checked. In case of disagreement, the two reviewers discussed or seek for a third-party solution. The contents of extraction include: 1) Basic characteristics of included researches: name of the first author, year of publication, country, etc. 2) Cohort level characteristic: researches design, number of patients in the case/control groups, population of the control type, mutation detection assay for LncRNA and sample sources. 3) Outcomes: number of true-positive, false-positive, false-negative, true-negative, sensitivity and specificity. Quality assessment was conducted by adapting the Quality Assessment of Diagnostic Accuracy Researches-2 (QUADAS-2) checklist and Newcastle-Ottawa Scale (NOS) scale. QUADAS-2 checklist scale contains 14 items, which were scored according to “yes (1 point)”, “no (0point)” and “unclear (0 point)”. NOS checklist scale contains 8 items, the full score is 9.

2.4 Statistical methods

Heterogeneity among researches was assessed by the Cochrane’s Q-test and I2 statistics. If the heterogeneity was considered statistically significant, the random-effect model was chosen for the meta-analysis, otherwise, the fixed-effect model was used. If Random effect model was used for statistical analysis, subgroup analysis was used to explore the source of heterogeneity. For the diagnostic meta-analysis, the correlated diagnostic accuracy indexes were collected as follows: sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odd ratio (DOR), and their corresponding 95% confidence intervals (CIs). summary receiver operating characteristic (SROC) curve and area under curve (AUC). The closer the AUC value was to 1, the diagnostic efficiency was higher. The publication bias was detected using Deeks’ regression test of asymmetry. All statistical analyses were performed by using Review Manager 5.2, Meta-Disc 1.4 and Stata 16.0 software.

3. Results

3.1 Collection and selection of literatures

A total of 346 publications were identified from the electronic databases using relevant search terms. This included 149 publications from PubMed, 196 publications from Embase and 1 publication from Cochrane Library. Firstly, 76 publications were excluded due to duplicated researches and 270 publications were further screened. Among 270 publications, a total of 160 publications were excluded after assessing the titles and abstracts, which involved 85 and 75 publications, respectively. Subsequently, 110 publications were assessed for the eligibility of meta-analysis. After excluding 92 publications according to the inclusion criteria stated, the remaining 18 publications were included in meta-analysis. The publication selection process was shown in Fig. 1. Finally, 18 researches were included in the meta-analysis with a total of 1587 patients with bladder cancer. All work was done individually by two investigators and disagreements arose to be assessed by a third researcher.

3.2 Publication bias

Publication bias is an important factor affecting the accuracy of diagnosis. Deeks’ funnel plot asymmetry test was performed to check publication bias in this meta-analysis. The result indicated that no significant bias was found ($p = 0.95$) (Fig. 2). Therefore, no obvious publication bias existed in the meta-analysis of diagnostic researches.

3.3 Baseline characteristics and quality assessment

The included publications were selected in the years from 2006 until 2020. Besides, the researches were mainly conducted in countries including China, Egypt, Iran and Israel. Based on Table 1, there were 28 markers selected in meta-analysis. These

markers were detected mostly using PCR detection methods in which the specimens were obtained from urine, blood and tissues. Table 1 shows the baseline characteristics of 18 included researches. A total of 1587 patients entered the final diagnostic analysis and 1636 patients served as controls. The control group mainly included healthy people and patients with benign diseases. Some research used the normal tissues of bladder cancer patients as the control group.

Table 1
Baseline characteristics and quality assessment of included articles.

Authors	Year	Country	Case	Control	Control Type	Target/Marker	Assay Methods	Specimen	NOS
Du et al	2018	China	120/110	120/110	Healthy	uc004cox.4; GAS5	PCR	Urine	8
Duan et al	2016	China	100	100	Healthy and benign urological disorders	MEG3; SNHG16; MALAT1	PCR	Blood	7
Eissa et al (1)	2015	Egypt	94	116	Healthy and benign urological disorders	Lnc-UCA1	PCR	Urine	7
Eissa et al	2019	Egypt	98	98	Healthy and benign urological disorders	lncRNA miR-497-HG; HOTAIR;	PCR	Urine	7
Abdolmaleki et al	2020	Iran	50	30	Healthy	NEAT1; TUG1; FAS-AS1;	PCR	Tissues	7
						PVT1; GHET1; HOTAIRM1			
Li et al	2019	China	56	56	Healthy	TUC338	PCR	Blood and tissues	8
Gielchinsky et al	2017	Israel	21	27	Healthy	H19	PCR	Urine	7
Abbastabar et al	2020	Iran	30	10	Healthy	ANRIL; PCAT-1	PCR	Urine	8
Srivastava et al	2014	India	117	74	Healthy and benign urological disorders	UCA1	PCR	Urine	6
Wang J et al	2018	China	52	104	Healthy and benign urological disorders	H19	PCR	Blood	6
Wang W et al	2017	China	96	96	Paired adjacent normal tissues	H19; UCA1; HOTAIR	PCR	Tissues	5
Wang X et al	2017	China	94	85	Healthy and benign urological disorders	UCA1	PCR	Urine	6
Yu et al	2020	China	140	140	Benign urological disorders	UCA1-201; HOTAIR; HYMA1; MALAT1	PCR	Urine	7

Yazarlou et al	2018	Iran	59	49	Healthy and benign urological disorders	UCA1-201; UCA1-203; MALAT1	PCR	Urine	5
Yuan S et al	2019	China	88	68	Healthy	LINC01638	PCR	Tissues	8
Zhang S et al	2019	China	100	100	Healthy	PCAT-1; UBC1; SNHG16	PCR	Blood	7
Zhen et al	2018	China	112	112	Paired adjacent normal tissues	CASC2a	PCR	Blood	6
Zheng R et al	2018	China	50	60	Healthy	PTENP1	PCR	Blood	7

The data was extracted by two authors independently from included researches. The following information were collected such as name of first author, year of publication, country, sample size, LncRNA target and markers, assay methods and specimen. Besides, the methodology quality of prognostic researches was assessed using the Newcastle-Ottawa Scale (NOS) tool. This NOS score ranged from 0 to 9. A higher NOS score indicated higher methodological quality. The scores of 18 articles were higher than five points. Furthermore, the Quality Assessment of Diagnostic Accuracy Researches-2 (QUADAS-2) was used to systematically assess the quality of all the included researches. The results showed that the scores of 18 articles were higher than eight points, suggesting that the quality of the literature was higher as a whole.

3.4 Heterogeneity analysis and threshold effect

In order to evaluate the heterogeneity of LncRNA included in the researches, the correlation coefficient and P value between the logarithm of true-positive rate and the logarithm of false-positive rate were calculated by Spearman test to exclude the threshold effect. Spearman correlation coefficient was 0.268 (P = 0.098 0.05). Also, the Cochran-Q value and I^2 value of the sensitivity and specificity outcomes were 238.26, 84.1%, P < 0.01 and 221.79, 82.9%, P 0.01, respectively. Indicating that there was no threshold effect. The above results indicate that heterogeneity existed among the researches, which may be related to population, regions, age, as well as different cut offs used across researches. Therefore, DerSimonian–Laird method is applied in this meta-analysis.

3.5 Diagnostic effect analysis

We use the random effects model to define the diagnostic performance, the pooled sensitivity (SEN) of all included LncRNA for the diagnosis of bladder cancer was 0.72 (95% CI, 0.70–0.73) (Fig. 3A), the pooled specificity (SPE) was 0.76 (95% CI, 0.75–0.78) (Fig. 3B), the positive likelihood ratio (PLR) of combined diagnosis was 3.09 (95% CI, 2.66–3.58) (Fig. 3C), The negative likelihood ratio (NLR) of combined diagnosis was 0.37 (95% CI, 0.33–0.42) (Fig. 3D), The combined diagnostic odds ratio (DOR) was 9.43 (95% CI, 7.30–12.20) (Fig. 3E). Indication, interpretations furthermore, the corresponding summary receiver operator characteristics (SROC) curve with an area under curve (AUC) was 0.82 (95% CI, 0.78–0.85) (Fig. 4). Among them, the researches of Eissa et al[22], Gielchinsky et al[23], Li G et al[24] and Wang XS et al[25] had the highest diagnostic effect, two of the researches used UCA1 as a marker, the remaining two researches used H19 and TUC338 as markers, respectively. Therefore, we believe that UCA1 and H19 may have the best diagnostic effect, which was confirmed in the subsequent subgroup analysis. More experiments are needed to verify the diagnostic effect of TUC338.

3.6 Subgroup analysis

A subgroup analysis was conducted using the source of specimen, regions of researches, control types, and markers. The pooled sensitivity (SEN), specificity(SPE), Positive likelihood ratio (PLR), Negative likelihood ratio (NLR), Diagnostic odds ratio (DOR) and Area under curve (AUC) for each subgroup analysis are depicted in Table 2, I2 and Q test were used to measure the heterogeneity.

Table 2
Subgroup analysis of diagnostic effect.

Subgroup	SEN			SPE			PLR	NLR	DOR	AUC	cases
	Values	I^2	P	Values	I^2	P					
Specimen											
urine	0.72(0.70–0.74)	86.2	0.00	0.81(0.79–0.83)	85.6	0.00	3.99	0.34	13.12	0.85	883
blood	0.72(0.69–0.75)	82.8	0.00	0.70(0.67–0.73)	66.9	0.00	2.46	0.38	6.88	0.78	470
tissues	0.70(0.67–0.74)	83.9	0.00	0.72(0.68–0.76)	64.1	0.00	2.50	0.41	7.34	0.79	234
Regions											
China	0.71(0.70–0.73)	79.8	0.00	0.75(0.74–0.77)	83.5	0.00	2.98	0.37	8.60	0.81	1118
Non-China	0.73(0.70–0.75)	88.4	0.00	0.79(0.76–0.82)	82.2	0.00	3.49	0.36	11.47	0.84	469
Control types											
Healthy	0.69(0.67–0.72)	81.9	0.00	0.76(0.74–0.79)	76.1	0.00	3.14	0.41	8.87	0.82	625
Benign and healthy	0.76(0.73–0.78)	85.2	0.00	0.76(0.73–0.79)	88.8	0.00	3.18	0.31	11.09	0.84	614
Others	0.71(0.68–0.74)	87.2	0.00	0.76(0.73–0.79)	86.7	0.00	2.97	0.37	8.80	0.81	348
Marker											
UCA1	0.80(0.77–0.83)	63.0	0.01	0.79(0.76–0.83)	92.6	0.00	4.04	0.26	16.85	0.85	600
H19	0.79(0.72–0.85)	60.2	0.08	0.73(0.66–0.78)	80.8	0.01	3.27	0.30	12.67	-	169
HOTAIR	0.60(0.55–0.66)	47.8	0.15	0.79(0.74–0.84)	72.9	0.03	2.87	0.50	6.05	-	286
MALAT1	0.67(0.61–0.72)	77.9	0.01	0.68(0.62–0.73)	0.0	0.96	2.07	0.50	4.09	-	299

In order to improve the diagnostic effect as well as to standardize subsequent experiments after this research to reduce heterogeneity among similar researches, and also to be able to better guide clinical applications, we explored the optimal specimen source. Subgroup analysis was performed using different specimen sources, the pooled SEN (0.72 vs 0.72 vs 0.70), SPE (0.81 vs 0.70 vs 0.72), PLR (3.99 vs 2.46 vs 2.50), NLR (0.34 vs 0.38 vs 0.41), DOR (13.12 vs 6.88 vs 7.34) and AUC (0.85 vs 0.78 vs 0.79) showed that the diagnostic effect of use specimen from urine in the diagnosis of bladder cancer is better than that of blood or tissue specimen. Considering that bladder cancer is derived from the urothelium, combined with the fact that urine specimens are more easily accessible, it is more reasonable and efficient to use LncRNA from urine specimen for the diagnosis of bladder cancer.

At the same time, we want to know whether our research is widely representative. In the literature included in this research, there are more papers published by Chinese authors. Therefore, we discussed the differences between Chinese researches and researches from other countries. Of the subgroups grouped by regions, the pooled sensitivity (0.71 vs 0.73), specificity (0.75 vs 0.79), PLR (2.98 vs 3.49), NLR (0.37 vs 0.36), DOR (8.60 vs 11.47) and AUC (0.81 vs 0.84) showed that the diagnostic effect of LncRNA in researches of other countries were slightly higher than those in Chinese researches, But the difference is not obvious. Therefore, we believe that the effect of using LncRNA to diagnose bladder cancer is not significantly different in distinct regions. And our research has wide applicability in different regions, especially in Asia, and has high reference value.

The use of different types of control groups will also affect the experimental results, in order to guide the follow-up experimental design and reduce the heterogeneity of the same type of researches, we performed subgroup analyses for researches that adopted different types. The results showed the highest sensitivity when employing benign and healthy controls (0.69 vs 0.76 vs 0.71), but the specificity was almost the same in the three subgroups (0.76 vs 0.76 vs 0.76). But in general, the researches using normal tissue adjacent to cancer as control group had the worst diagnostic effect (DOR (8.87 vs 11.09 vs 8.80), AUC (0.82 vs 0.84 vs 0.81)). In addition, considering the collection of tissue specimens as an invasive diagnostic method, whether in the follow-up experiments or clinical applications, there are difficulties in sampling, so it is not an ideal way to use the normal tissue adjacent to cancer as the control group. Combined with the previous data, using the urine specimens of patients with benign diseases or healthy people as the control group can get the best diagnosis effect.

Finally, we hope to find one or more biomarkers with high diagnostic effect, but most of the biomarkers do not have enough similar researches, so we can't carry out systematic analysis. Therefore, when a single marker has three or more identical researches, we also performed subgroup analysis. We analyzed four markers, UCA1, H19, HOTAIR and MALAT1. The results show that UCA1 and H19 had a higher sensitivity (0.80 vs 0.79 vs 0.60 vs 0.67), but UCA1 and HOTAIR had a higher specificity (0.79 vs 0.73 vs 0.79 vs 0.68). Overall, UCA1 and H19 had higher diagnostic effect (DOR (16.85 vs 12.67 vs 6.05 vs 4.09)). This is consistent with our previous prediction. UCA1 and H19 are very valuable diagnostic markers for bladder cancer. Subsequent researches can use these two markers to build panel for joint diagnosis of bladder cancer.

3.7 Clinical utility

The overall distribution of the researches is summarized in Fig. 5. To obtain the post-test probability, a simulation of an environment that had a prevalence of 20% for bladder cancer was performed, with base on the included researches. The analysis was performed by incorporating the evidence in a Fagan's nomogram. As shown in Fig. 5, the nomogram showed that the positive post-test probability was 44% and the negative post-test probability was 8%. It is suggested that LncRNA is of great significance in the early diagnosis of bladder cancer. At the same time, we also analyzed UCA1, which was also simulated in an environment with a bladder cancer prevalence of 20%, the nomogram showed that the positive post-test probability was 50% and the negative post-test probability was 6%. The results showed that the diagnostic effect of UCA1 for bladder cancer was higher than the average level of all LncRNA. It is an excellent diagnostic marker for bladder cancer.

4. Discussion

Nowadays, a growing number of researches have indicated the important roles of LncRNA in bladder cancer, as LncRNA affects many physiological processes of bladder cancer, such as proliferation, migration, invasion, apoptosis and so on[20, 26]. This research aims to find new markers that can be used as noninvasive diagnosis of bladder cancer, leading to reduced compliance with cystoscopy, less patient distress, and lower financial burden for patients. LncRNA can be detected in blood, urine and tissues[27]. Many kinds of LncRNA are found to be different between healthy people and patients with bladder cancer. It can be used as a molecular marker for the early detection and treatment of bladder cancer[28, 29]. However, in order

to apply LncRNA to clinical diagnosis, we need to establish standards, including sampling methods, sample processing, detection and analysis methods, and need to determine an optimal cut-off parameter.

To analyze the efficacy of LncRNA in the diagnosis of bladder cancer, 18 researches were included in this research. Our work found that the sensitivity and specificity of LncRNA were 0.72(0.70–0.73) and 0.76(0.75–0.78) respectively, and AUC was 0.82(0.78–0.85). The positive likelihood ratio of LncRNA in the diagnosis of bladder cancer was 3.09(2.66–3.58), the negative likelihood ratio was 0.37(0.33–0.42), and the combined diagnostic odds ratio was 9.43(7.30–12.20). The above data fully prove that LncRNA detection has a high application value in the diagnosis of bladder cancer. It can well replace the urine cytology diagnosis and become a new method of non-invasive diagnosis of bladder cancer. The researches data of Du et al[30] can also confirm this. Combined with its advantages of simple, fast and low cost, it is of great significance for the screening of early bladder cancer. At the same time, it can also be used as a monitoring means for patients with bladder cancer after the operation, which can relieve the pain of repeated cystoscopy and reduce the huge economic burden. Besides, it will improve the compliance and survival rate of patients along with improving the quality of life after operation.

We explored the impact of specimen from different sources on the diagnostic effect and found that detection of LncRNA expression in urine specimen has a better diagnostic effect than detection of LncRNA expression in blood and tissue. It may be due to the fact that bladder cancer cells are more likely to shed cells into the urine which further release LncRNA in it. The latest expert opinion also believes that urine markers for the diagnosis of bladder cancer are of great significance[28]. Therefore, in order to use LncRNA for clinical diagnosis in the future, we highly recommend to use urine as a standard sampling method.

At the same time, we are also very interested in whether there are differences in researches in different regions. Therefore, we conducted a subgroup analysis of China researches and researches from other countries. The results show that the diagnostic effect of LncRNA in researches from other countries is slightly higher than that in Chinese researches, but we still think that Chinese researches is closer to the real situation, because the sample size of Chinese researches is larger (1118 vs 469) However, the heterogeneity among all the researches in China is still very high. We think that the main source of heterogeneity is that we analyzed different LncRNAs together. In addition, all the researches did not clearly specify the cut-off value, which led to a high degree of heterogeneity.

The selection of different control types also has a certain impact on the final results. Our researches results show that the diagnosis effect of patients with benign diseases and healthy people as the control group is the best, and the use of benign diseases and healthy people as the control group is more in line with the clinical application scene. Therefore, in future researches, we suggest that researchers should use patients with benign diseases and healthy people as the control group.

Finally, some LncRNA markers have been studied by multiple authors, and we have analyzed these LncRNA individually as well. We analyzed a total of four LncRNA, UCA1, H19, HOTAIR, and MALAT1. Among them, UCA1 was the most reported, and 6 researchers reported it. Increasing evidence suggests that UCA1 has been highly expressed in bladder cancer cells [31, 32]. Moreover, UCA1 has the specificity of expression in bladder cancer tissues. Its expression in other urinary tumors is very low, while it does not express in corresponding para cancerous tissues, normal bladder tissues and normal kidney tissues[25, 33]. Therefore, it is very suitable as a diagnostic marker of bladder cancer. Our analysis also shows that UCA1 has a high diagnostic effect (Table 2), it has the highest sensitivity and specificity among the four markers we analyzed alone. we also analyzed H19, HOTAIR and MALAT1 separately, which showed good diagnostic performance. However, due to the limitation of sample size, more studies are needed to support our conclusion. In addition to single LncRNA, some LncRNA combinations can significantly improve the diagnostic performance. For example, Duan et al[34] found that the diagnostic performance of LncRNA combinations (MEG3, SNHG16 and MALAT1) for TA, T1 and T2-T4 was significantly higher than that of urine cytology. Therefore, based on the investigations of single LncRNA, it will be a more advanced research direction to explore the LncRNA combination that can be used for the diagnosis of bladder cancer.

Although our results are very encouraging, we should also consider several limitations of this study, such as since this meta-analysis revolved around the Asian countries notably China, the results discussed would not be an ideal reference for the other areas of the world. Besides, there was high heterogeneity between the included researches. We could not perform further analysis of the heterogeneity of the researches deeply. Furthermore, the cut-off point of the included references was not included due to the inconsistency of the cut-off point in each research. All included papers determined different types of LncRNA, thus contributing to the heterogeneity in the results analyzed. As some of the included studies did not provide sufficient data, we estimated the best sensitivity and specificity under the ROC curve using Engauge Digitizer 11 software. This could affect the reliability of finalized results.

5. Conclusions

To sum up, the current data analysis results show that LncRNA can be used for early diagnosis and postoperative monitoring of bladder cancer, especially for urine samples, as it can effectively reduce the physiological pain and economic burden of patients with bladder cancer. Although, this study has summarized the diagnostic effects of several LncRNAs reported so far, among them, UCA1 and H19 are identified with the best diagnostic effect, and now it is still necessary to expand the sample size to further verify the diagnostic effect of LncRNA.

Abbreviations

BC
Bladder cancer, SEN:sensitivity, SPE:specificity, PLR:positive likelihood ratio, NLR:negative likelihood ratio, DOR:diagnostic odd ratio, CIs:confidence intervals, SROC:summary receiver operating characteristic curve, AUC:area under curve, QUADAS-2:Quality Assessment of Diagnostic Accuracy Researches-2, NOS:Newcastle-Ottawa Scale.

Declarations

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Author Contributions

Y.C. and F.N. designed the experiments. Y.C. and F.N. searched and screened the articles respectively, and H.L. assessed the divergence between the two authors. Z.Z. and M.S. evaluated the quality of the literature respectively, and S.F. assessed the divergence between the two authors. Y.C. extracted and analyzed the data. F.N. wrote the paper. S.F., H.L. and J.H. revised the paper. Z.Y. and H.W. initiated the research and organized, designed, and revised the paper.

Competing Interests

The authors have declared that no competing interest exists.

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Figures

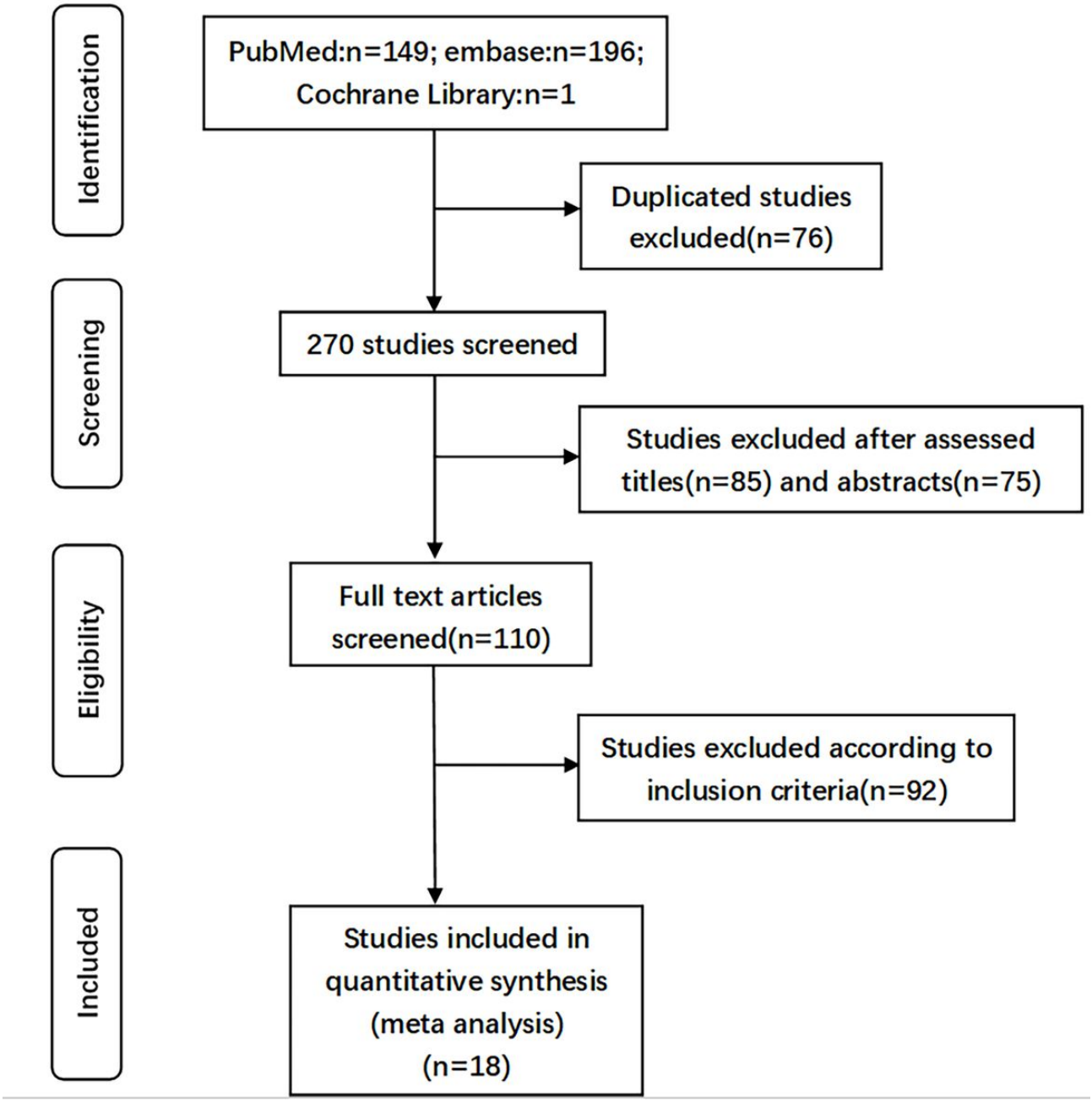

Figure 1

Flow chart of publication search and selection.

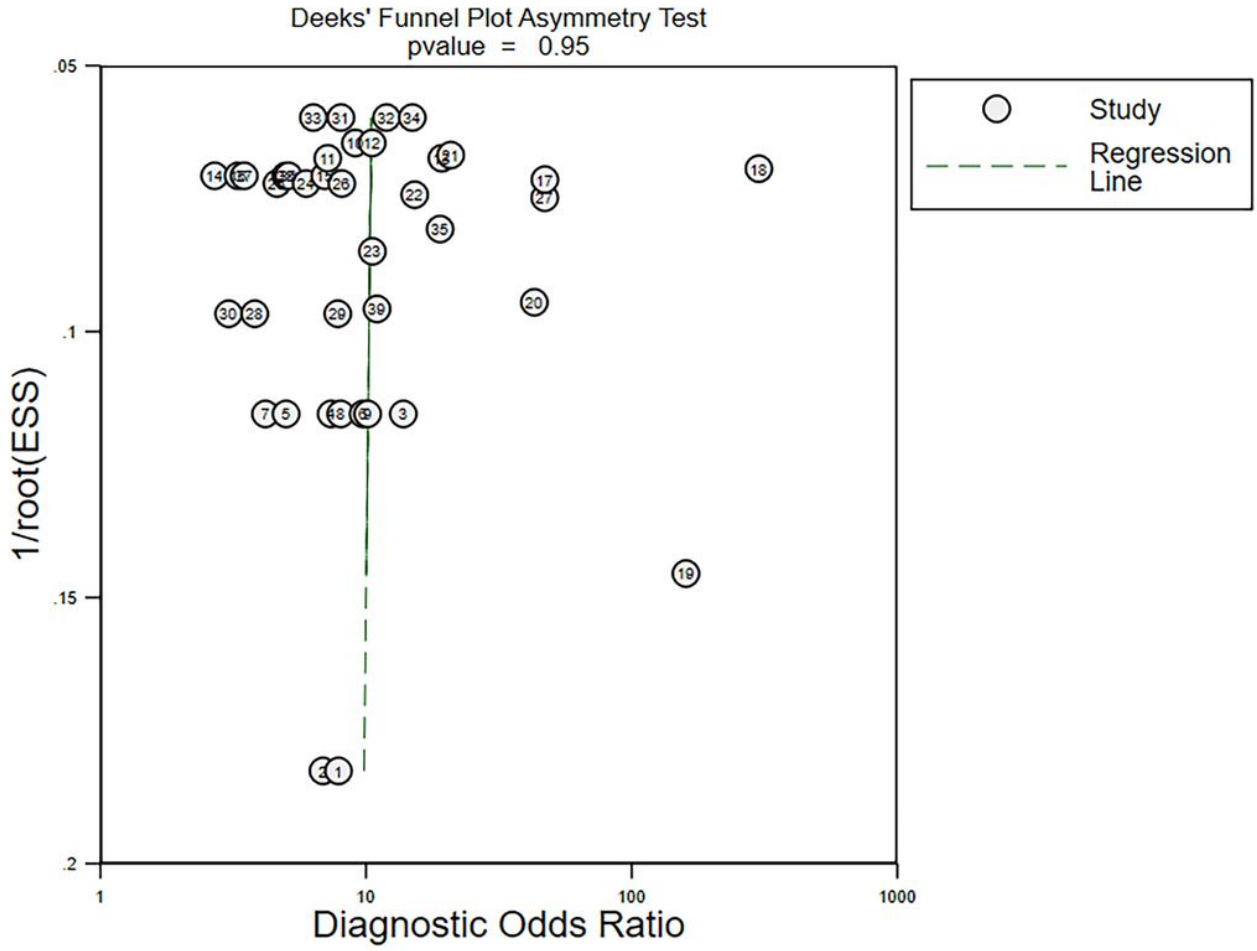

Figure 2

Publication bias from Deek's test for LncRNA assay in the diagnosis of bladder cancer.

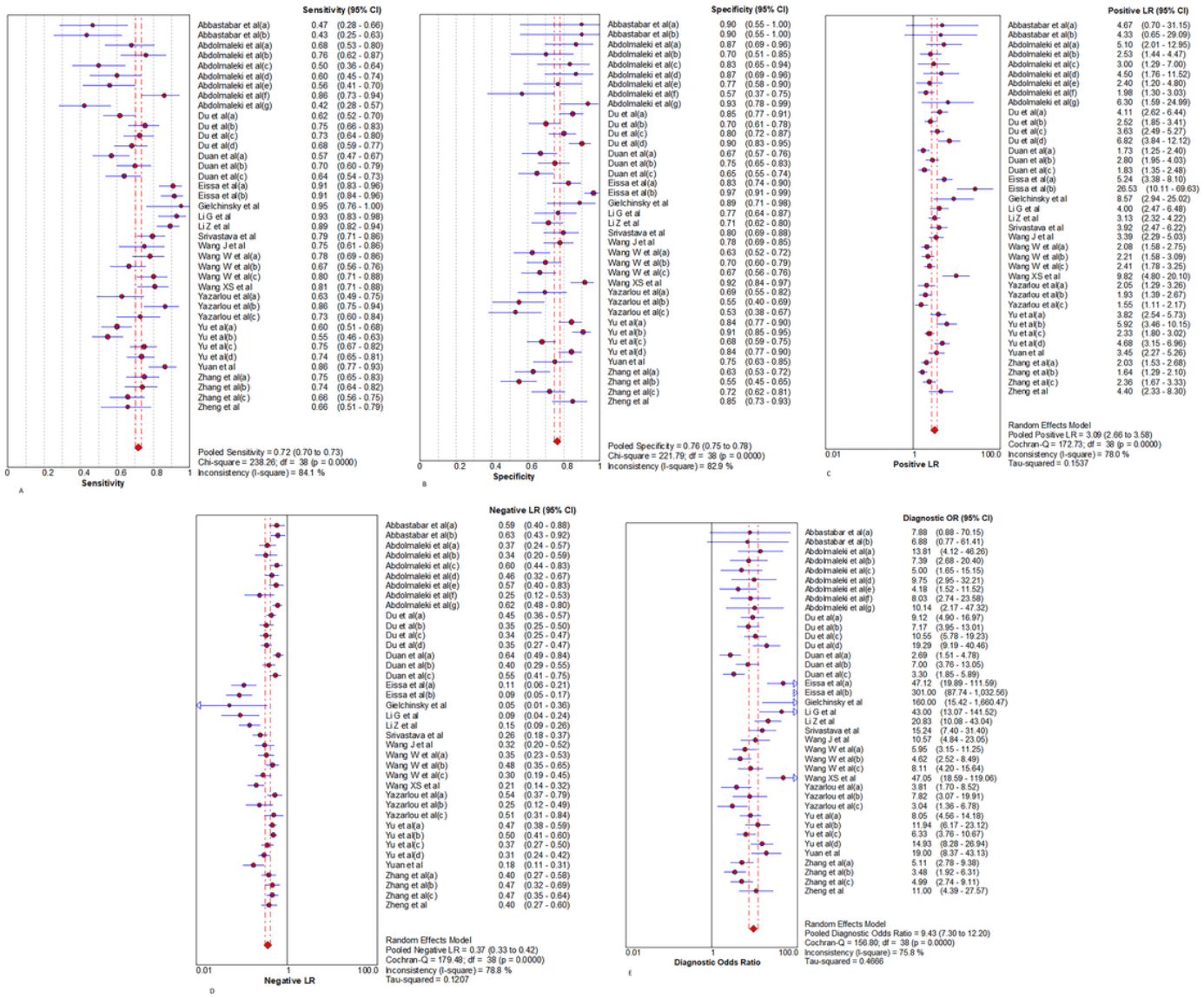

Figure 3

Results of overall pooled diagnostic performance for LncRNA in bladder cancer. (A) Forest Plot of Pooled Sensitivity Analysis, (B) Forest Plot of Pooled Specificity Analysis, (C) Forest Plot of Pooled Positive LR Analysis, (D) Forest Plot of Pooled Negative LR Analysis, (E) Forest Plot of Pooled Diagnostic OR Analysis.

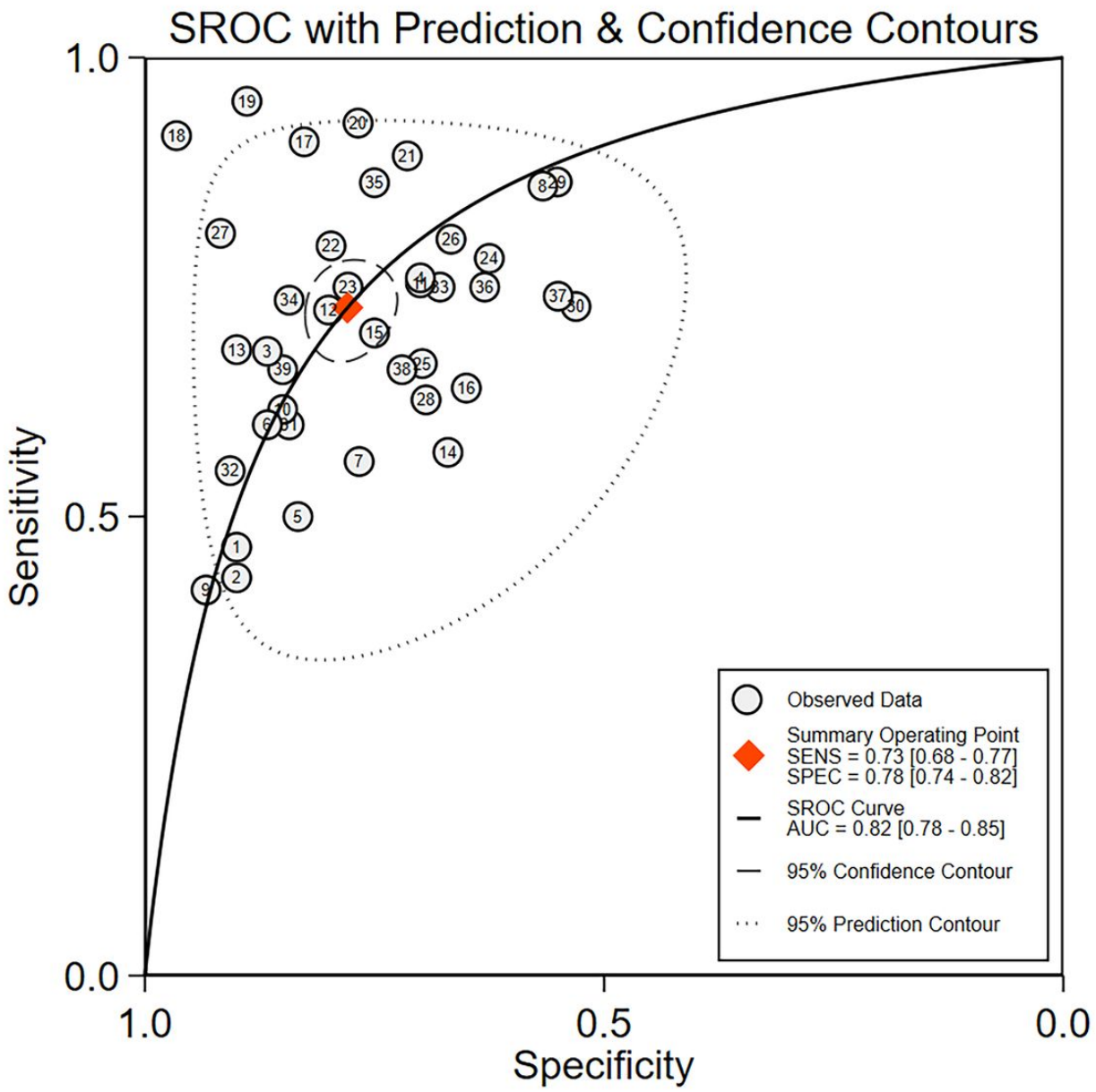

Figure 4

The ROC curve for LncRNA in the diagnosis of bladder cancer patients in all patients.

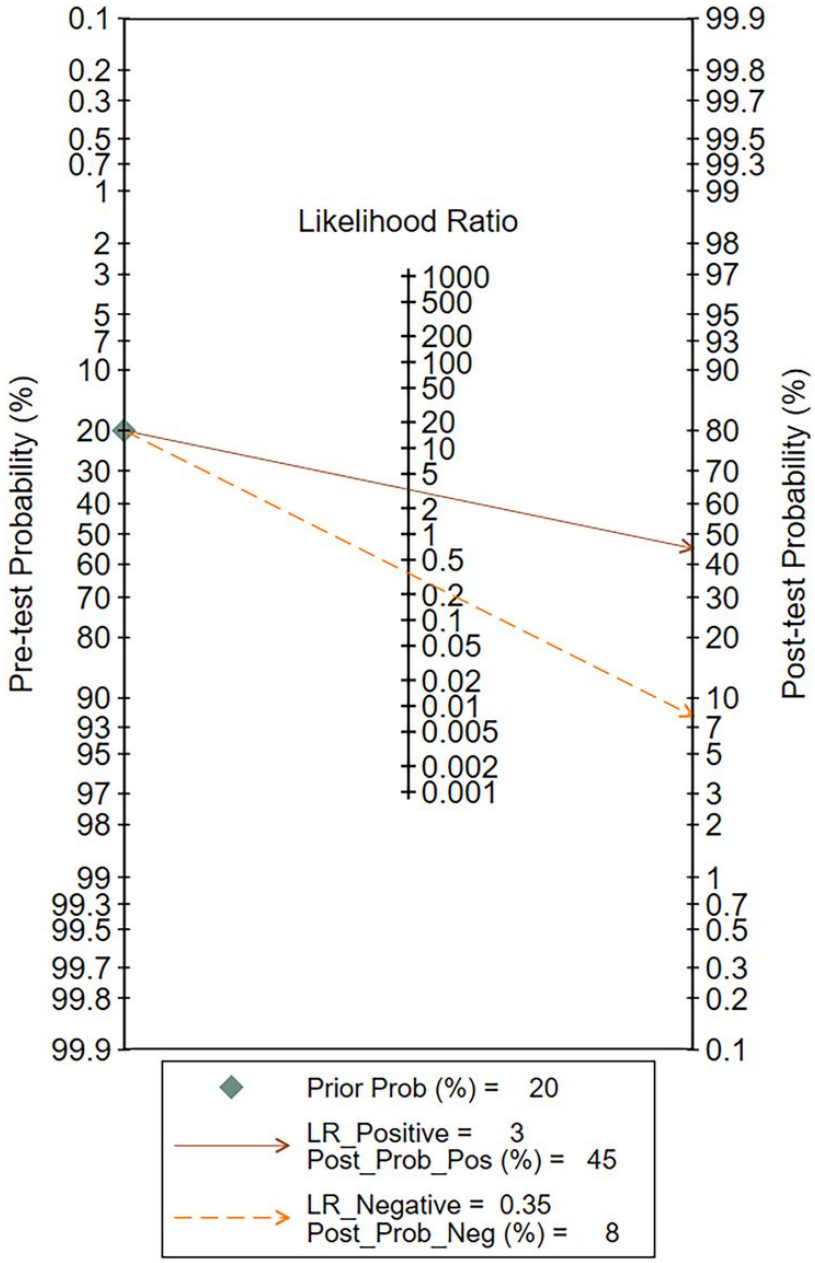

Figure 5

Fagan's nomogram describes the ability of LncRNA assay to confirm or exclude patients with bladder cancer.