Systematic Review and Meta-Analysis

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lncRNA-UCA1 in the diagnosis of bladder cancer

A meta-analysis

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Abstract

Background: The main purpose of this study is to systematically evaluate the diagnostic value of long-chain non-coding RNA urothelial carcinoembryonic antigen 1 (lncRNA-UCA1) for bladder cancer, and to provide a scientific basis for the diagnosis of bladder cancer.

Methods: By searching PubMed, Web of Science, EMBASE, CNKI, Wanfang, Weipu and other databases, in order to collect relevant literature of lncRNA-UCA1 for diagnosis of bladder cancer. The starting and ending time of the search is from the establishment of the database to December 31, 2019. Screen documents and extract data according to inclusion and exclusion criteria. QUADAS entry tool was used to evaluate the quality of literature. Meta-Disc 1.4 and Stata 12.0 software were used for statistical analysis, and UCA1 was combined for the statistics of bladder cancer diagnosis.

Results: A total of 7 articles were included in this study, including 954 cases of bladder cancer patients and 482 cases of non-bladder cancer patients. The receiver operating characteristic curve (ROC) curve AUC of lncRNA-UCA1 used to diagnose bladder cancer was 0.86. The sensitivity was 0.83 (95% CI: 0.80–0.85), and the specificity was 0.86 (95% CI: 0.82–0.89). The positive likelihood ratio is 6.38 (95% CI: 3.01–13.55), and the negative likelihood ratio is 0.20 (95% CI: 0.13–0.31). The diagnostic odds ratio is 33.13 (95% CI: 11.16–98.33).

Conclusion: lncRNA-UCA1 has a high value of clinical auxiliary diagnosis for bladder cancer, and it can be further promoted and applied clinically.

Abbreviations: dOR = diagnostic odds ratio, lncRNA-UCA1 = long-chain non-coding RNA urothelial carcinoembryonic antigen 1, MDR = multidrug resistance, NLR = negative likelihood ratio, PLR = positive likelihood ratio, ROC = receiver operating characteristic curve, UCA1 = urothelial carcinoembryonic antigen 1.

Keywords: bladder cancer, diagnosis, lncRNA-UCA1, meta-analysis, urothelial carcinoembryonic antigen 1

1. Introduction

Bladder cancer is a common malignant tumor of the urinary system, and its global incidence ranks fourth in male malignant tumors and tenth in female malignant tumors.[1–3] The incidence of bladder cancer increases with age, and the global incidence of bladder cancer has shown an upward trend in recent years.[4]

Editor: Chien-Feng Li.

This article does not contain any studies with human participants.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Ding Z, Ying W, He Y, Chen X, Jiao Y, Wang J, Zhou X. lncRNA-UCA1 in the diagnosis of bladder cancer: a meta-analysis. Medicine 2021;100:11(e24805).

Received: 12 November 2020 / Received in final form: 28 January 2021 / Accepted: 29 January 2021

http://dx.doi.org/10.1097/MD.0000000000024805

Bladder cancer is one of the common malignant tumors of the urinary system, which seriously threatens people's health.[5,6] At present, the clinical detection of bladder cancer is mainly cystoscopy and pathological biopsy, but cystoscopy is a invasive examination, which is more painful and has the risk of bleeding and infection.[7] When diagnosing micro-cell carcinoma, its sensitivity is low and it is easy to miss diagnosis. Therefore, we need to find some sensitive and specific examination methods to assist cystoscopy and pathological biopsy, so that the early diagnosis of bladder cancer is more accurate, simple, low trauma and economically feasible.

At present, the diagnostic methods of bladder cancer mainly include cystoscopy, random bladder biopsy and urine cytology.[8–10] However, the first 2 methods are invasive and uncomfortable, and the sensitivity of cytological examination is low due to the high variability between observers. Long-chain non-coding RNA urothelial carcinoembryonic antigen 1 (lncRNA-UCA1) has potential application value in the diagnosis of bladder cancer, but its diagnostic value is still controversial due to differences in sample size and population among studies.[11] Cystoscopy is the most important method for diagnosing bladder cancer, and it is often used in combination with urine cytology.[12,13]

Cystoscope is an invasive test, and urine cytology has a high specificity (96%), but its detection sensitivity is low (44%) (especially in the diagnosis of low-grade malignant tumors).[8,14] Urothelial carcinoembryonic antigen 1 (UCA1) is a long-chain non-coding RNA (lncRNA) highly expressed in bladder cancer tissues.[15] lncRNA-UCA1 is the first lncRNA found in bladder

cancer, there are obvious expression differences in different tumor tissues, especially in digestive and urogenital tumors.[16] The study found that lncRNA-UCA1 may be a potential marker for bladder cancer diagnosis.[17–19] Studies have shown that lncRNA-UCA1 is highly specific in the diagnosis of bladder cancer.[15,20] In particular, it has a very high sensitivity for cases of bladder cancer stage G2-G3, suggesting that lncRNA-UCA1 is helpful for the early diagnosis of bladder cancer.[13,21] This study intends to systematically evaluate the diagnostic efficacy of lncRNA-UCA1 for bladder cancer through quantitative Meta analysis, and then provide a scientific basis for the diagnosis of bladder cancer.

2. Materials and methods

2.1. Search strategy

The words of "lncRNA-UCA1", "UCA1", "bladder", "cancer", "carcinoma, "diagnosis" were as search keywords by searching PubMed, Web of Science, EMBASE, CNKI, Wanfang, Weipu and other electronic databases. The retrieval period is from Chinese to English documents from the database establishment to December 31, 2019. This article does not contain any studies with human participants.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) The research object was patients with bladder cancer diagnosed clinically. (2) The study clearly defined the types and number of cases and controls. (3) The study provides enough data to directly or indirectly construct a 2×2 diagnostic quadruple table. Exclusion criteria: (1) Non-clinical diagnostic research, such as basic research, review, case report, letter, comment, meeting summary, etc. (2) The data provided cannot construct a 4-diagnosis table for diagnosis. (3) Repetitively published papers.

2.3. Data extraction

Two researchers independently extracted the content of the literature, and the results of the mutual check were consistent. The extracted data include: title, first author, publication year, sample size (including control group and case group), cut-off value, sample type, internal reference gene type and test method.

2.4. Quality evaluation of included literature

The QUADAS-2 scale was used to evaluate the quality of literature. According to the relevant questions included in each part (7 items in total), answer "yes", "no" and "unsure" Corresponding to each item, the risk level of bias is determined as "low (1 point)", "high (2 point)" or "uncertain (0 point)". The total score of 7 items is ≥4 points, which means that the quality of literature research is high.

2.5. Statistical method

Meta-Disc 1.4 and Stata 12.0 software were used for Meta analysis. Combine sensitivity, specificity, diagnostic odds ratio (dOR), positive likelihood ratio (PLR) and negative likelihood ratio (NLR), and summarize receiver operating characteristic curve (ROC) curve and its corresponding 95% CI. Spearman rank correlation, Cochran-Q and I^2 tests were used to evaluate the heterogeneity between studies. $P < .05$ or $I^2 > 50\%$ suggested that there was heterogeneity between studies. When there is heterogeneity between studies, a random effect model is used to combine statistics.[22,23] Explore the sources of heterogeneity through subgroup analysis and sensitivity analysis. The funnel chart was used to analyze publication bias, and $P < .05$ was considered to be a publication bias between studies.[24]

3. Results

3.1. Literature screening and quality assessment

A total of 172 related documents were retrieved, and 4 duplicate documents were excluded according to the inclusion and exclusion criteria. By reading the title and abstract, 16 articles were finally retained for full text evaluation. Furthermore, 9 non-conforming documents were excluded, and 7 studies were finally included for meta-analysis.[9,25–30]

This study included 954 cases of bladder cancer patients and 482 cases of non-bladder cancer patients. The characteristics of the included literature are shown in Table 1. The QUADAS-2 entry was used to evaluate the quality of the included literature. The included 7 articles all have a QUADAS score higher than 4 points, suggesting that the quality of the study is high.

3.2. Various indicators of bladder cancer diagnosis by lncRNA-UCA1

Because of the heterogeneity between the studies, a random effects model was chosen to incorporate the effects. The ROC curve AUC of lncRNA-UCA1 used to diagnose bladder cancer was 0.86, the combined sensitivity was 0.83 (95% CI: 0.80–0.85), the specificity was 0.86 (95% CI: 0.82–0.89), positive LR

Table 1

General characteristics of included studies.

Study	Year of publication	Country	Identification methods	Reference gene	QUADAS scores	Cut-off value	Case/control	UCA1 test			
								TP	FP	FN	TN
Wang et al[29]	2006	China	qRT-PCR	G3PDH	10	0	94/85	76	7	18	78
Zhang et al[28]	2012	China	qRT-PCR	G3PDH	10	NA	180/144	152	11	28	133
Srivastava et al[27]	2014	India	qRT-PCR	GAPDH	7	NA	117/28	93	6	24	22
Eissa et al[25]	2015	Egypt	qRT-PCR	GAPDH	10	1.09	184/36	169	2	15	34
Eissa et al[26]	2015	Egypt	qRT-PCR	GAPDH	10	1.09	150/60	137	2	13	58
Milowich et al[19]	2015	Belgium	qRT-PCR	TBP	8	NA	161/65	113	19	48	46
Zhang et al[30]	2018	China	qRT-PCR	GAPDH	10	0.762	68/64	52	22	16	42

qRT-PCR = reverse transcription-PCR.

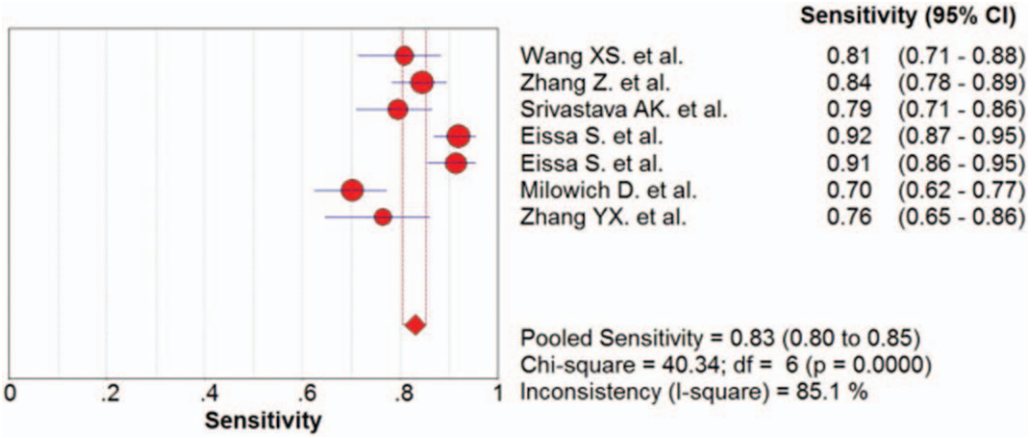

Figure 1. Plot of sensitivity.

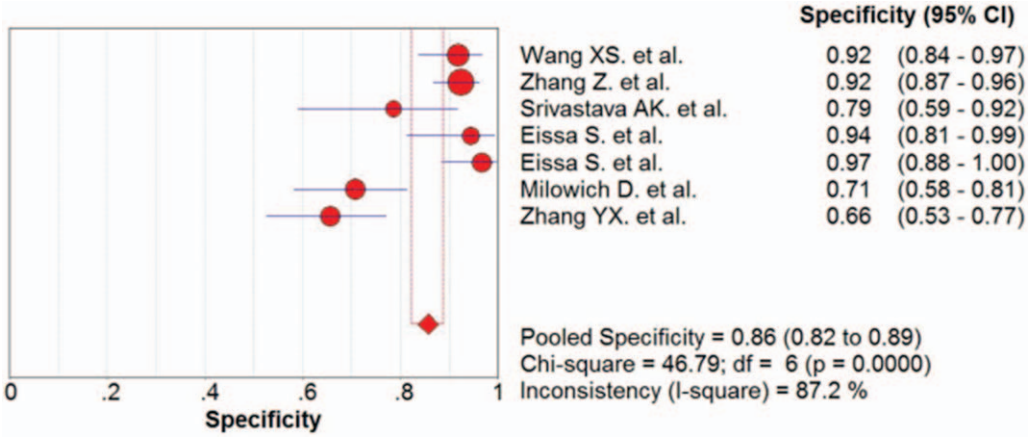

Figure 2. Plot of specificity.

is 6.38 (95% CI: 3.01–13.55), negative LR is 0.20 (95% CI: 0.13–0.31), and dOR is 33.13 (95% CI: 11.16–98.33). The results of statistical analysis are shown in Figures 1–6 and Table 2.

3.3. Heterogeneity analysis and publication bias

After Spearman analysis, the correlation coefficients $r = -0.929$, $P = .003$, suggesting that this study has a threshold effect and the heterogeneity caused by it. The heterogeneity generated by the

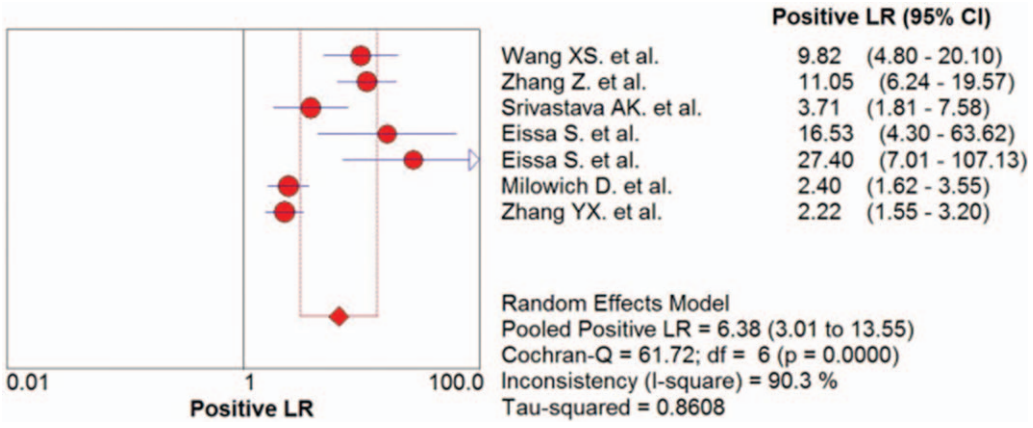

Figure 3. Plot of positive LR.

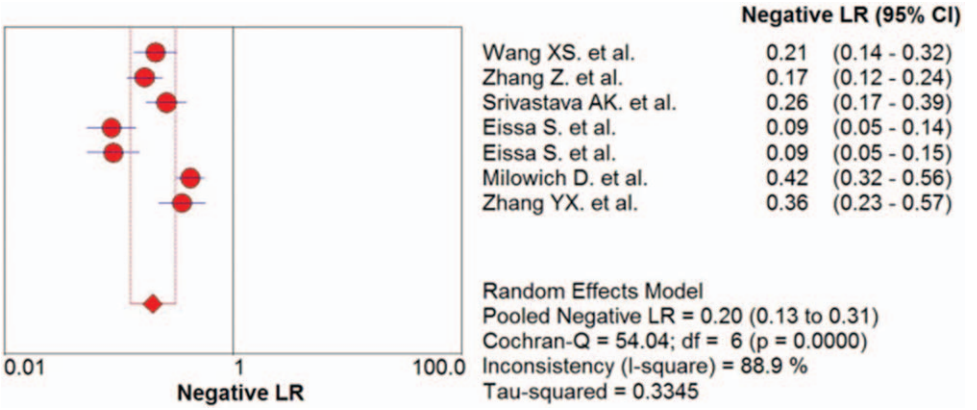

Figure 4. Plot of negative LR.

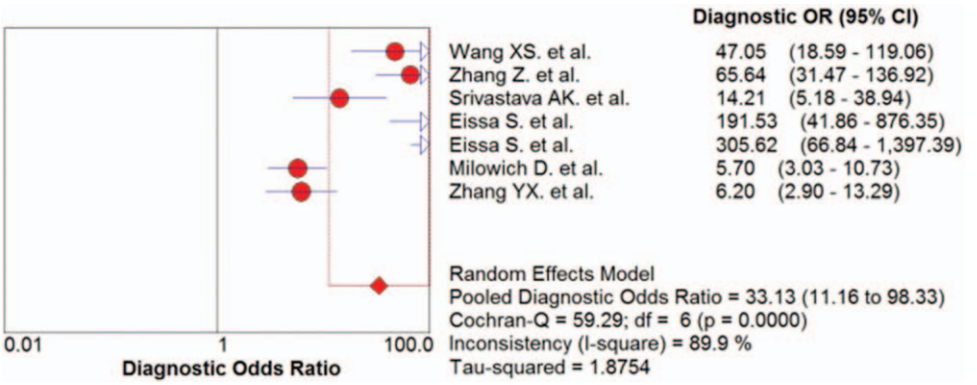

Figure 5. Plot of diagnostic OR.

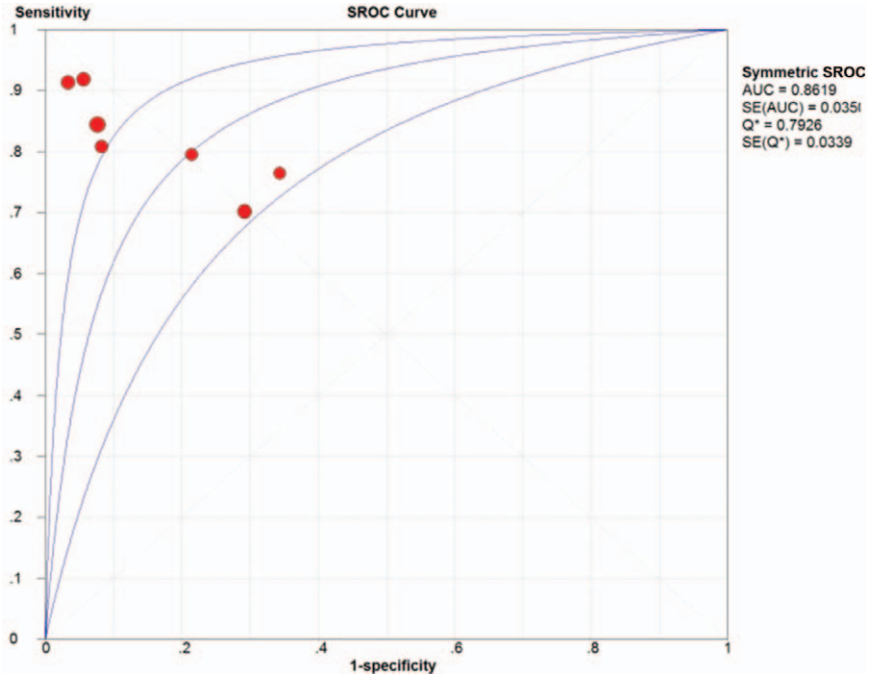

Figure 6. Plot of SROC curve.

Table 2

lncRNA-UCA1 indicators for the diagnosis of bladder cancer.

	Test of association		Test of heterogeneity				Egger's test for publication bias	
Parameter	Estimates	95% CI	*Q*	*P* value	I^2 (%)	Model	*t*	*P* value
Overall	–	–	36.51	<.01	86.5	Random	1.58	.17
Sensitivity	0.83	0.80 to 0.85	40.34	<.01	85.1	–	–	–
Specificity	0.86	0.82 to 0.89	46.79	<.01	87.2	–	–	–
Positive LR	6.38	3.01 to 13.55	61.72	<.01	90.3	Random	–	–
Negative LR	0.2	0.13 to 0.31	54.04	<.01	88.9	Random	–	–
dOR	33.13	11.16 to 98.33	59.29	<.01	89.9	Random	–	–

dOR = diagnostic odds ratio, LR = likelihood ratio.

threshold effect was evaluated by the Cochran-*Q* value and the I^2 test value. The results showed that Cochran-$Q = 36.51$, $P = .001$, $I^2 = 86.5\%$, indicating that there was heterogeneity caused by the threshold effect. There is no publication bias in this study, and the statistical analysis results are shown in Table 2.

4. Discussion

As the most common malignant tumor of the urogenital system, bladder cancer has a high annual morbidity and mortality, and it gradually increases with age.[31,32] About 75% of bladder cancer is non-muscle invasive bladder cancer, and the 5-year survival rate is 88% to 98% .[33–35] The 5-year survival rate of muscular invasive bladder cancer is only 46% to 63%, and more than 70% of patients will still relapse after treatment.[17,36,37] The incidence and mortality of bladder cancer are on the rise. Therefore, it is very important for the early diagnosis and clear diagnosis of bladder cancer patients. At present, the early diagnosis methods mainly include clinical manifestations, urinary exfoliation cytology, optical imaging, tumor marker detection, imaging examination, cystoscopy biopsy, and pathological examination after diagnostic electrotomy.

Tumor markers related to bladder cancer are affected by various factors, and the positive rate is low, which limits the clinical application.[38] Exploring new types of tumor markers needs to consider their sensitivity, specificity, noninvasiveness, and simplicity, and is less affected by adverse factors. Through multidirectional research and joint testing can make up for each other's deficiencies and improve the diagnostic accuracy, but the cost is too high. Therefore, finding new tumor markers for bladder cancer has become a new development direction. The occurrence of multidrug resistance (MDR) in tumors is considered to be one of the important reasons leading to the recurrence and metastasis of bladder cancer and poor prognosis.[39] MDR is a unique and broad-spectrum drug resistance phenomenon, after a type of anti-tumor drug makes tumor cells resistant, other anti-tumor drugs with different structures and different mechanisms of action can also make tumor cells cross-resistant.[40,41]

The combined sensitivity of this study was 0.83, the specificity was 0.86, and the AUC was 0.86, suggesting that lncRNA-UCA1 is a very valuable biological marker in the diagnosis of bladder cancer. In addition, the dOR value can explain the degree of correlation between diagnosis and disease.[20–22] In addition, the combined PLR was 6.38, suggesting that compared with patients without cancer, lncRNA-UCA1 was 6 times more effective in the diagnosis of bladder cancer. NLR is 0.20, suggesting that lncRNA-UCA1 may have a false positive rate of 20% in the diagnosis of bladder cancer, suggesting that it is not enough to completely exclude bladder cancer. The SROC curve is located near the upper left corner with an AUC of 0.86, suggesting that lncRNA-UCA1 is of high diagnostic value in bladder cancer.

This study also has certain limitations. First of all, there are obvious heterogeneities in this study, which are mainly caused by the threshold effect. Because the different types of internal reference genes involved have different effects on the diagnosis of bladder cancer, this may be the main source of heterogeneity. In addition, due to the small number of studies of lncRNA-UCA1 (n = 7), there may be unpublished literature that affects the diagnostic value of lncRNA-UCA1 in this study. At the same time, only one of the sample types included in this study is of organizational origin, and its inclusion in the total study may increase the heterogeneity of the combined statistics.

In conclusion, this study confirmed that lncRNA-UCA1 is a new type of non-invasive tumor marker with high sensitivity and specificity, and has certain clinical auxiliary diagnostic value for bladder cancer. lncRNA-UCA1 can be used as an auxiliary biomarker for early diagnosis of bladder cancer.

Author contributions

ZSD is responsible for the study design, definition of intellectual content, data analysis, manuscript preparation & editing; WWY is responsible for the literature research, data analysis, manuscript preparation; YHH is responsible for the literature research, data acquisition, statistical analysis; XC is responsible for the data acquisition, statistical analysis; YTJ is responsible for the data acquisition, statistical analysis; JFW is responsible for the data acquisition; XFZ is responsible for the guarantor of integrity of the entire study, study concepts, manuscript review. All authors read and approved the final manuscript.

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Writing – review & editing: Zhenshan Ding, Xiaofeng Zhou.

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