

The relationship between long non-coding RNAs and clinical metastasis as well as prognosis of renal cell carcinoma patients: a meta-analysis

Yang Su

Department of Urology, The First Affiliated Hospital of Anhui Medical University

Shun Xu

Department of Urology, The First Affiliated Hospital of Anhui Medical University

Cheng Wu

Department of General Surgery, The First Affiliated Hospital of Anhui Medical University

Li Zhang

Department of Urology, The First Affiliated Hospital of Anhui Medical University

Song Fan

Department of Urology, The First Affiliated Hospital of Anhui Medical University

Jun Zhou

Department of Urology, The First Affiliated Hospital of Anhui Medical University

Chaozhao Liang (✉ liang_chaozhao@ahmu.edu.cn)

Department of Urology, The First Affiliated Hospital of Anhui Medical University

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Abstract

Background: Recently, some lncRNAs in studies were also regarded as the potential prognostic biomarkers for renal cell carcinoma. The aim of this meta-analysis is to evaluate the prognostic significance of lncRNAs for RCC and explore their correlation with lymph node metastasis (LNM) and distant metastasis (DM).

Methods: A series of electronic databases were chosen to retrieve the eligible articles. A total of 35 studies involving 3535 patients with RCC were included finally. The statistical analysis was performed using STATA 16.0 and review manager 5.3 software. The relative risk (RR) and hazard ratio (HR) with 95% confidence interval (CI) were calculated to assess the significance. The stratified subgroup analysis was conducted by the up-regulated group and down-regulated group. Additionally, the sensitivity analysis was performed by the sequential omission of individual studies, and the publication bias was detected using Begg's test.

Results: The results indicated lncRNAs expression levels were correlated with LNM for up-regulated lncRNAs (RR=2.06, 95% CI: 1.53-2.78, $p<0.00001$) and down-regulated lncRNAs (RR=0.49, 95% CI: 0.31-0.76, $p=0.002$). The expression levels of lncRNAs were closely related to DM (RR=1.67, 95% CI: 1.21-2.29, $p=0.002$). Moreover, the expression levels of these lncRNAs were also associated with the overall survival (HR=1.71, 95% CI: 1.28-2.28, $P=0.0003$).

Conclusions: This meta-analysis suggested that lncRNAs could be regarded as biomarkers for clinical lymph node metastasis or distant metastasis and also may serve as the potential predictive factors of prognosis for RCC.

Background

Renal cell carcinoma (RCC) is one of the most common cancers, which accounts for approximately 2%-3% of all human cancers. It is the third most common in genitourinary cancers. Recently, it has been reported that about 100,000 people died worldwide due to RCC. Unfortunately, the incidence of RCC is still increasing at a rate of 2%-2.5% every year¹⁻⁴. As we all know, there are many subtypes of renal cell carcinoma. Clear cell renal cell carcinoma (ccRCC) is the most common subtype of RCC. The proportion of ccRCC is approximate 60%-85%, followed by papillary RCC (pRCC), then the chromophobe RCC (chRCC) and others⁵⁻⁹. RCC is generally insensitive to chemotherapy and radiotherapy¹⁰⁻¹¹. Surgery is the golden standard and may be the only effective method for early or localized RCC patients¹². With the application of some advanced medical instruments such as multi-dimensional color Doppler ultrasound and multi-row computed tomography, nearly one-third of RCC patients have been founded with clinical metastasis which would lead to a poor prognosis at the first hospital-visit. The mean survival period of these patients is usually less than one year¹³. The tumorigenic mechanism of RCC is truly complicated. Although several studies have shown that many genetic changes and epigenetic dysregulations were associated with the progression and prognosis of RCC, the molecular mechanism of renal cell carcinoma pathogenesis was still unclear and needed to be further studied. So far, none specific and sensitive molecular biomarkers for RCC have been declared. Previous studies have indicated that many molecules such as Von Hippel-Lindau (VHL), hypoxia inducible factor (HIF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF), erythropoietin (EPO) and Ki-67 were closely related to the early diagnosis, relapse, metastasis and survival of renal cell carcinoma¹⁴⁻¹⁷. However, the accuracy of these molecular biomarkers is limited, it is still unable to precisely assess the progression, metastasis and recurrence risk of renal cell carcinoma. Therefore, the identification of novel biomarkers and even therapeutic targets is urgently needed.

About 80% of the human genome was estimated to be transcribed while only 1%-2% was protein-encoded. The non-coding portions of the genome transcription products are non-coding RNAs [1]. The famous and newly discovered non-coding RNA among them via microarray or high-throughput RNA sequencing is long non-coding RNA [2]. The length of their transcripts are usually more than 200 nucleotides. They lack functional open reading frames, so they could not be translated into proteins. However, they actively play a role in various cellular biological processes, such as cellular proliferation, differentiation, death, stem cell pluripotency, gene damage response and chromosomal imprinting [3-6]. Meanwhile, accumulating evidences indicated that lncRNAs were closely associated with many human diseases, including tumorigenesis and development such as hepatocellular carcinoma [7], gastric carcinoma [8], colon cancer [9], thyroid cancer [10], lung cancer [11] and so on. They act as either oncogenes or tumor suppressors and regulate multiple physiological or pathological processes. However, the underlying mechanism is still needed to be further explored.

Recently, some lncRNAs in studies were also regarded as the potential prognostic biomarkers for renal cell carcinoma [12-14]. However, single study may be not accurate and sufficient because of sample size and other limitations. Therefore, it is better to systematically analyze these studies to determine their potential clinical values for RCC. In this meta-analysis, we will summarize and analyze lncRNAs that are associated with the metastasis and prognosis of RCC patients to evaluate their clinical application values.

Methods

Literature search strategy

In this meta-analysis, we searched four international databases including Web of Science, PubMed, Embase and Medline electronic library without time limitation. To increase the sensitivity, we used MeSH terms and free-text words in the search strategy. The key or text words were used as follows: (lncRNA OR lncRNAs OR lincRNA OR lincRNAs OR "long noncoding RNA" OR "long noncoding RNAs" OR "long non-coding RNA" OR "long non-coding RNAs" OR "long intergenic noncoding RNA" OR "long intergenic noncoding RNAs" OR "long intergenic non-coding RNA" OR "long intergenic non-coding RNAs") AND (cancer OR cancers OR carcinoma OR neoplasm OR tumor OR tumors OR tumour OR tumours OR malignancy) AND (renal OR kidney OR "renal cell carcinoma" OR "renal cell cancer" OR RCC OR "kidney cancer" OR "renal cancer" OR "kidney carcinoma" OR "renal carcinoma"). The species in researches was limited to human and the language was restricted as English.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies that investigated RCC patients or cancer patients including RCC; (2) the expression levels of lncRNAs in tumor tissues were measured by quantitative real time polymerase chain reaction (qRT-PCR) or other methods and divided into two forms: high and low; (3) the relationship between lncRNAs expression and clinical metastatic features as well as survival outcomes were reported; (4) The hazard ratio (HR) for overall survival (OS) were provided in studies; (5) HR with 95% CI and *p* value could be obtained or calculated from data in articles.

The exclusion criteria were as follows: (1) letters, editorials, expert opinions, case reports and reviews; (2) non-English articles; (3) non-human species; (4) only cell or serum without human tissue was investigated; (5) lacking usable data or original data; (6) studies with duplicated data; (7) lncRNAs expression levels were not distinguished; (8) studies without clinical metastasis characteristics and survival outcome; (9) HR was calculated in the form of multiple lncRNAs or estimated from insufficient data.

Data extraction

Data from these eligible studies were extracted independently by two investigators (Su and Xu). These data retrieved from each article contained the following information: the last name of the first author, the publication year, the investigated lncRNA name, nationality of research objects, number of patients, type of cancer, stage of cancer, sample style, lncRNA detection method, number of high and low lncRNA expression group as well as patients with lymph node metastasis and distant metastasis in each group and HR with 95% CI for overall survival or other survivals. Normally, these data were obtained from the original article, if unavailable, we contacted the corresponding author to collect them.

Statistical analysis

The relationship between lncRNAs expression levels and lymph node metastasis or distant metastasis as well as prognosis of RCC patients was assessed by HR and RR with 95% CI. The heterogeneity was evaluated by Q test and I^2 test. For the Q test and I^2 statistic respectively, it was considered significant if *P* value was less than 0.1 or I^2 was more than 50%. A random-effect model was used to calculate the pooled HR or RR if $I^2 \geq 50\%$ or $P < 0.1$, otherwise, a fixed-effect model was utilized. Furthermore, in order to reduce the influence of existing heterogeneity, we performed subgroup analysis. In this meta-analysis, statistical analyses of HR for prognosis and the RR for LNM and DM were calculated by Review Manager Version 5.3 (RevMan, the Cochrane Collaboration). Meanwhile, the Stata Software 16.0 (Stata, College Station) was also used to assess the sensitivity and publication bias. *P* value less than 0.05 was considered to be statistically significant.

Results

Characteristics of eligible studies

As shown in Figure 1, a total of 672 records about lncRNA expression and human cancer were retrieved in PubMed, Web of Science, Embase and Medline electronic databases according to our settings. 619 records among them were excluded after reviewing the titles and abstracts. Subsequently, remaining 53 full-text articles were assessed for eligibility, and 18 studies were further excluded because of the irrelevant analysis. Finally, 35 articles were chosen for this meta-analysis. Among these 35 studies, the specific cancer we concerned was human renal cell carcinoma; 33 articles came from China and 2 came from Japan; all the metastasis were diagnosed by pathology; all the tissue specimens were well preserved before RNA extraction.

Clinical features

The basic research features and related results about metastasis and prognosis from the 35 including studies were listed in Table 1. A total of 3535 participants from China and Japan were involved in these 35 studies. Among these 35 articles, 28 studies reported the lymph node metastasis or distant metastasis or both. However, only 11 studies reported overall survival (OS).

Among these lncRNAs, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [15-17], H19 [18], promoter of CDKN1A antisense DNA damage activated RNA (PANDAR) [19], renal cell carcinoma related transcript-1 (RCCRT1) [20], protein sprouty homolog 4 intronic transcript-1 (SPRY4-IT1) [21], nuclear paraspeckle assembly transcript 1 (NEAT1) [14, 22], HOX transcript antisense RNA (HOTAIR) [13, 23], cytoskeleton regulator RNA (linc00152) [24], Small nucleolar RNA host genes 3,5,6 (SNHG3,5,6) [25-28], AGAP2-AS1 [29], Epidermal growth factor receptor-antisense 1 (EGFR-AS1) [30], Titin-antisense 1 (TTN-AS1) [31], ZNF1-antisense 1 (ZFA1) [32], Plasmacytoma variant translocation 1 (PVT1) [33], Lung cancer-associated transcript 1 (LUCAT1) [34], Gastric carcinoma high expressed transcript 1 (GHET1) [35], The HOXA transcript at the distal tip (HOTTIP) [36], Transforming growth factor-b (ATB) [37], High-expressed in renal cell carcinoma (HEIRCC) [38] and taurine up-regulated 1 (TUG1) [9, 39] were up-regulated while PGM5-AS1 [40], Serum deprivation response-antisense (SDPR-AS) [41], DUXAP10 [42], lncRNA downregulated in liver cancer stem cells (lncRNA-DILC) [43], DHRS4-AS1 [44], LOC389332 [45], neuroblastoma associated transcript 1 (NBAT1) [46] and T-cell leukemia/lymphoma 6 (TCL6) [12] were down-regulated.

As for the methods used to detect lncRNA expression levels in tumor tissues, all studies used qRT-PCR. The cut-off values were various in these studies due to the different cut-off definitions. Finally, all these studies did not report that these lncRNAs were significantly associated with age and gender of patients. However, some studies showed that lncRNAs were significantly correlated to tumor size [17], histological grade [18] or tumor stage [14].

Relationship between lncRNAs expression levels and LNM

The 28 selected studies reported a total number of 921 patients with LNM in the form of different lncRNA expression levels. These studies have passed the Q test and the I^2 test ($I^2 = 79\%$, $P < 0.00001$), which indicated that the heterogeneity was significant. Labbe Graph and Galbraith Plot for heterogeneity were shown

in Figure 2A and Figure 2B. The random-effects models were selected, and the RR was 1.43 (95% CI: 1.10-1.86, $P=0.008$) (Figure 2C), which means the incidence of LNM in the lncRNA high expression group was 1.43 times that in the low expression group, and it was statistically significant. Visual inspection of the Begg's funnel plot revealed symmetry (Figure 2D). The symmetry of the above funnel plot was tested, and the result showed no publication bias ($P=2.31$) (Figure 2E).

Due to the significant heterogeneity, we explored the reasons for heterogeneity via sensitivity analysis (Figure 2F) and meta regression (Figure 2G). It was suggested that the up-regulated group and the down-regulated group were the sources of heterogeneity. Therefore, we performed subgroup analysis to these studies (Figure 2H). As for the up-regulated lncRNAs subgroup (RR=2.06, 95% CI: 1.53-2.78, $P<0.00001$), high lncRNA expression had a significant elevated LNM rate compared with low lncRNA expression. On the contrary, low lncRNA expression had a significant increased LNM rate compared with high lncRNA expression in the down-regulated lncRNAs subgroup (RR=0.49, 95% CI: 0.01-0.53, $P=0.002$).

The publication bias test was performed to the subgroups. As shown in Figure 2I and Figure 2J, a publication bias was found in the up-regulated group ($P=0.000$). For the asymmetric funnel plot of the up-regulated group, the trim and fill analysis was selected for correction, and 8 articles were finally virtualized. After the trim and fill analysis, no publication bias was found in the up-regulated group (Figure 2K and Figure 2L).

Relationship between lncRNAs expression levels and DM

Likewise, all chosen studies reported a total number of 730 patients with DM according to the different lncRNA expression levels. Labbe Graph and Galbraith Plot for heterogeneity were shown in Figure 3A and Figure 3B. As the heterogeneity was also significant ($I^2=78\%$, $P=0.00001$), a random-effects model was still adopted. As shown in Figure 3C, the results indicated that high lncRNA expression versus low lncRNA expression, had a statistic significant elevated DM rate for the up-regulated lncRNAs subgroup (RR=1.67, 95% CI: 1.21-2.29, $P=0.002$). Visual inspection of the Begg's funnel plot revealed asymmetry (Figure 3D). The asymmetry of the above funnel plot was tested, and the result displayed a publication bias ($P=0.002$) (Figure 3E). For the asymmetric funnel plot of the eligible studies, the trim and fill analysis was selected for correction, and 5 articles were finally virtualized. After the trim and fill analysis, no publication bias was found in the up-regulated group (Figure 3F and Figure 3G).

We also explored the reasons for heterogeneity via sensitivity analysis (Figure 3H) and meta regression (Figure 3I). The results suggested that up/down regulation was not the source of heterogeneity and was not statistically significant.

Relationship between lncRNAs expression levels and prognosis

11 studies including 1850 patients reported the relationship between lncRNAs expression levels and prognosis (OS) of RCC patients in this meta-analysis. Due to the significant heterogeneity ($I^2=73\%$, $P<0.0001$), the random-effects model was used. As shown in Figure 4A, lncRNA expression levels were closely related to OS (HR=1.71, 95% CI: 1.28-2.28, $P=0.0003$) of RCC patients. Moreover, high lncRNA expression had a significant reduced clinical survival compared with low lncRNA expression. Visual inspection of the Begg's funnel plot revealed symmetry (Figure 4B). The symmetry of the above funnel plot was tested, and the result showed no publication bias ($P=0.448$) (Figure 4C).

We also explored the reasons for heterogeneity via sensitivity analysis (Figure 4D) and meta regression (Figure 4E). The results suggested that up/down regulation was not the source of heterogeneity and was not statistically significant.

Publication bias, sensitivity analysis and meta regression

We used Stata 16.0 software to evaluate the sensitivity, publication bias and meta regression. In this meta-analysis, Begg's test was used in publication bias due to the possible excessive assessment. Meanwhile, the sensitivity analysis was also used to assess the reliability and stability of the combined results and to see whether the individual study affected the overall results. Finally, meta regression was used to explore the causes of heterogeneity.

Discussion

In recent years, a large number of studies have focused on lncRNAs and explored their biological mechanism and molecular function [47, 48]. Increasing evidences showed the potential relationship between the aberrant expression of lncRNAs and cancers [49, 50]. That is to say, the up-regulation or down-regulation of some lncRNAs contributed to tumorigenesis and progression by affecting their cellular processes. However, the underlying mechanism involved in regulating cancers metastasis and prognosis remain unclear. In order to find some effective treatments and molecular biomarkers for RCC, this systematic meta-analysis was performed. It was firstly to systematically analyze the association between lncRNA expression and clinical metastatic features as well as prognosis of RCC patients.

In this meta-analysis, we investigated the metastatic features and prognostic roles of lncRNAs in RCC by using the subgroup analysis. Meanwhile, the sensitivity analysis, publication bias and meta regression were also performed to optimize the statistical credibility. We found that dysregulated NEAT1 [14, 22], HOTAIR [13, 23], LOC389332 [45], MALAT1 [15-17], TCL6 [12], NBAT1 [46] could be viewed as biomarkers for lymph node metastasis while H19 [18], RCCRT1 [20], SPRY4-IT1 [21], TUG1 [9, 39] could be regarded as biomarkers for distant metastasis in RCC patients. That indicated high or low lncRNA expression in RCC tissues was significant correlated with either LNM or DM. In addition, we also found that 10 high expressed lncRNAs were associated with the poor OS, while 1 low expressed lncRNA was correlated to the poor OS in RCC patients. Therefore, all of these results suggested that these lncRNAs could serve as the novel independent predictive factors of clinical metastasis and poor prognosis for RCC.

Strengths and limitations of this study: (1) This is the first meta-analysis reporting the relationship between long non-coding RNAs and clinical metastasis as well as prognosis of renal cell carcinoma patients. (2) We used strict, broad search strategy of the internet databases to minimise any potential publication

bias. (3) The number of eligible studies may be small. (4) All research objects were Asian. (5) Due to lack of follow-up, the time subgroup analysis could not be performed.

Conclusions

In summary, this meta-analysis summarized current related researches. It was also the first one to evaluate the relationship between lncRNAs aberrant expression and RCC patients metastasis (LNM, DM) as well as prognosis (OS). The analysis revealed that lncRNAs not only could be considered as guideline for lymph node metastasis and distant metastasis, but could be regarded as potential prognostic biomarkers for RCC patients. However, more and larger-scale and higher quality researches should be performed to confirm the clinical values of lncRNAs for RCC due to the existing limitations here.

Abbreviations

LNM: lymph node metastasis; DM: distant metastasis; OS: overall survival; RCC: renal cell carcinoma; HE: high expression; LE: low expression; HLMN: high expression with lymph node metastasis; LLNM: low expression with lymph node metastasis; HDM: high expression with distant metastasis; LDM: low expression with distant metastasis; lncRNA: long non-coding RNA; HR: hazard ratio; ccRCC: clear cell renal cell carcinoma; FT: frozen tissue; PFS: progression-free survival; NA: not available; qRT-PCR: Real-time quantitative-Polymerase Chain Reaction; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; PANDAR: promoter of CDKN1A antisense DNA damage activated RNA; RCCRT1: renal cell carcinoma related transcript-1; SPRY4-IT1: protein sprouty homolog 4 intronic transcript-1; NEAT1: nuclear paraspeckle assembly transcript 1; HOTAIR: HOX transcript antisense RNA; linc00152: cytoskeleton regulator RNA; SNHG3,5,6: Small nucleolar RNA host genes 3,5,6; EGFR-AS1: Epidermal growth factor receptor-antisense 1; TTN-AS1: Titin-antisense 1; ZFAS1: ZNF1-antisense 1; PVT1: Plasmacytoma variant translocation 1; LUCAT1: Lung cancer-associated transcript 1; GHET1: Gastric carcinoma high expressed transcript 1; HOTTIP: The HOXA transcript at the distal tip; ATB: Transforming growth factor-b; HEIRCC: High-expressed in renal cell carcinoma; TUG1: taurine up-regulated 1; SDPR-AS: Serum deprivation response-antisense; lncRNA-DILC: lncRNA downregulated in liver cancer stem cells; NBAT1: neuroblastoma associated transcript 1; TCL6: T-cell leukemia/lymphoma 6

Declarations

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Authors' contributions

Conceptualization, YS and CZL; Formal analysis, SX and CW; Investigation, YS, SX and LZ; Methodology, SF; Resources, YS and CZL; Supervision, JZ and SF; Writing – original draft, YS and SX; Writing – review & editing, CZL and LZ. All authors read and approved the final manuscript.

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Availability of data and materials

All data used in this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China. ²Institute of Urology, Anhui Medical University, Hefei, China.

³Anhui Province Key Laboratory of Genitourinary Diseases, Anhui Medical University, Hefei, China.

⁴Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China.

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Table

Table 1: The basic information and clinical features of studies

Publication year	LncRNAs	Country	Sample number(n)	Tumor type	Tumor stage	Sample style	Detection method	Case number(n)						Survival analysis
								HE	LE	HLNM	LLNM	HDM	LDM	
2015	H19	China	92	ccRCC	T1-T4	FT	qRT-PCR	42	50	15	4	9	2	OS
2017	HOTAIR	China	43	ccRCC	T1-T4	FT	qRT-PCR	32	11	21	3	14	2	OS
2016	linc00152	China	77	ccRCC	I-IV	FT	qRT-PCR	38	39	NA	NA	8	12	OS
2017	LOC389332	China	30	ccRCC	T1-T4	FT	qRT-PCR	9	21	0	20	NA	NA	OS
2015	MALAT1	China	106	ccRCC	T1-T4	FT	qRT-PCR	46	60	13	6	5	9	OS
2015	NBAT-1	China	98	ccRCC	T1-T4	FT	qRT-PCR	49	49	3	11	NA	NA	OS
2017	PANDAR	China	62	ccRCC	I-IV	FT	qRT-PCR	34	28	4	0	3	0	OS
2014	RCCRT1	China	40	ccRCC	T1-T4	FT	qRT-PCR	24	16	6	0	9	0	PFS
2014	SPRY4-IT1	China	98	ccRCC	T1-T4	FT	qRT-PCR	52	46	13	1	14	2	OS
2017	TCL6	China	71	ccRCC	T1-T4	FT	qRT-PCR	36	35	0	7	0	6	OS
2017	TUG1	China	203	ccRCC	T1-T4	FT	qRT-PCR	100	103	29	13	32	15	OS
2015	MALAT1	Japan	50	ccRCC	T1-T4	FT	qRT-PCR	25	25	4	0	3	0	OS
2017	NEAT1	China	102	RCC	T1-T4	FT	qRT-PCR	68	34	36	6	NA	NA	OS, PFS
2020	AGAP2-AS1	China	537	ccRCC	T1-T4	FT	qRT-PCR	NA	NA	NA	NA	NA	NA	OS
2018	MALAT1	China	318	ccRCC	T1-T4	FT	qRT-PCR	217	101	132	51	NA	NA	OS
2019	EGFR-AS1	China	204	ccRCC	T1-T4	FT	qRT-PCR	102	102	NA	NA	21	10	OS
2019	PVT1	China	25	ccRCC	T1-T4	FT	qRT-PCR	13	12	8	6	NA	NA	OS
2019	PGM5-AS1	China	182	ccRCC	T1-T4	FT	qRT-PCR	92	90	18	34	19	31	OS
2018	LUCAT1	China	90	ccRCC	T1-T4	FT	qRT-PCR	NA	NA	NA	NA	NA	NA	OS
2017	HOTTIP	China	57	ccRCC	T1-T4	FT	qRT-PCR	334	195	183	107	74	33	OS
2018	SNHG6	China	81	ccRCC	T1-T4	FT	qRT-PCR	46	35	32	11	NA	NA	OS

	2017	ATB	China	198	ccRCC	T1-T4	FT	qRT-PCR	102	96	66	77	67	79	OS
	2017	NEA T1	China	76	ccRCC	T1-T4	FT	qRT-PCR	37	39	18	2	14	1	OS
	2017	sDPr-as	China	56	ccRCC	T1-T4	FT	qRT-PCR	21	35	10	28	NA	NA	OS
	2020	SNHG6	China	65	ccRCC	T1-T4	FT	qRT-PCR	NA	NA	NA	NA	NA	NA	OS
	2019	SNHG5	China	52	ccRCC	T1-T4	FT	qRT-PCR	38	14	18	2	14	1	NA
	2020	TTN-AS1	China	145	ccRCC	T1-T4	FT	qRT-PCR	65	80	NA	NA	26	22	NA
	2020	DUXAP10	China	18	ccRCC	T1-T4 T1-T4	FT	qRT-PCR	128	128	8	0	9	1	NA
	2019	lnc-DILC	China	68	ccRCC	T1-T4	FT	qRT-PCR	33	34	13	22	NA	NA	NA
	2019	SNHG3	China	36	ccRCC	T1-T4	FT	qRT-PCR	262	262	10	5	50	29	OS
	2018	GHET1	China	40	ccRCC	T1-T4	FT	qRT-PCR	29	11	NA	NA	22	9	NA
	2019	ZFAS1	China	60	ccRCC	T1-T4	FT	qRT-PCR	30	30	19	10	NA	NA	NA
	2018	DHRS4- AS1	China	52	ccRCC	T1-T4	FT	qRT-PCR	26	26	3	9	2	2	NA
	2016	HEIRCC	China	60	ccRCC	T1-T4	FT	qRT-PCR	28	42	7	3	9	3	NA
na	2017	HOTAIR	China	43	ccRCC	T1-T4	FT	qRT-PCR	21	43	5	0	8	4	NA

Figures

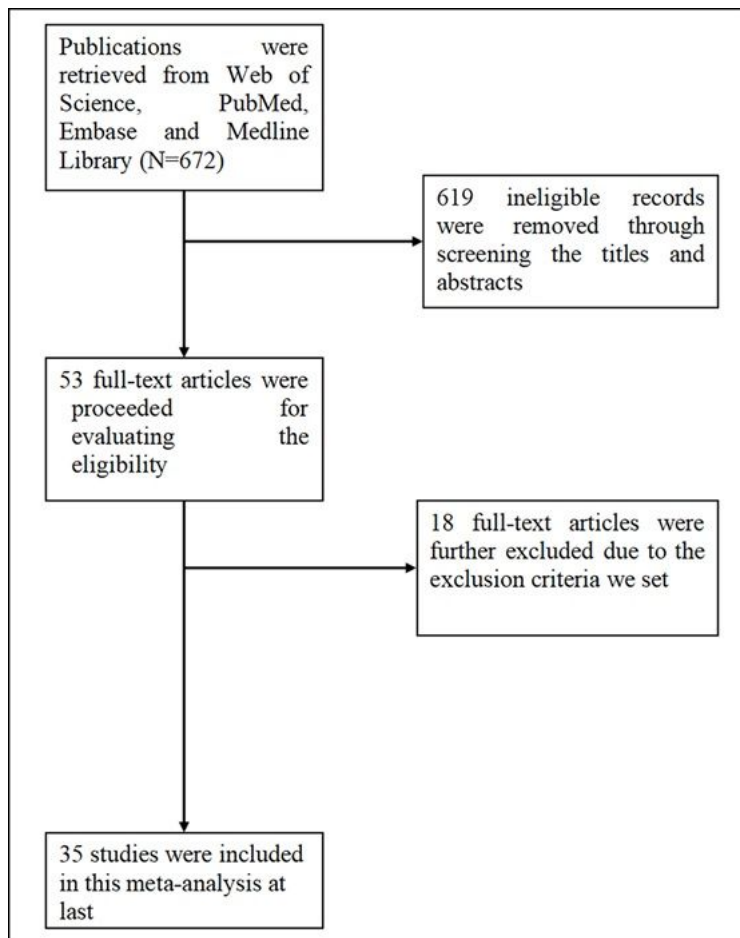


Figure 1

The flow diagram of study process.

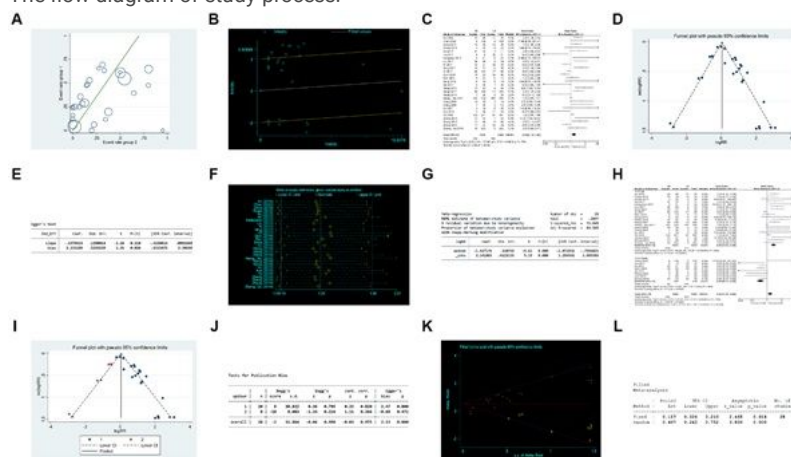


Figure 2

Relationship between lncRNAs expression levels and LNM. (A) Labbe graph for heterogeneity. (B) Galbraith plot for heterogeneity. (C) The forest plot of the relationship between lncRNAs expression levels and LNM for RCC. (D) The publication bias qualitative analysis of the eligible studies with LNM via Begg's test. (E) The publication bias quantitative analysis of the eligible studies with LNM via Begg's test. (F) The sensitivity analysis of the eligible studies with LNM. (G) The meta regression of the eligible studies with LNM. (H) subgroup analysis of the relationship between lncRNAs expression levels and LNM for RCC. (I) The publication bias qualitative analysis of the up-regulated group and the down-regulated group with LNM via Begg's test. (J) The publication bias quantitative analysis of up-regulated group and the down-regulated group with LNM via Begg's test. (K) Trim and fill qualitative analysis of the up-regulated group with LNM. (L) Trim and fill quantitative analysis of the up-regulated group with LNM.

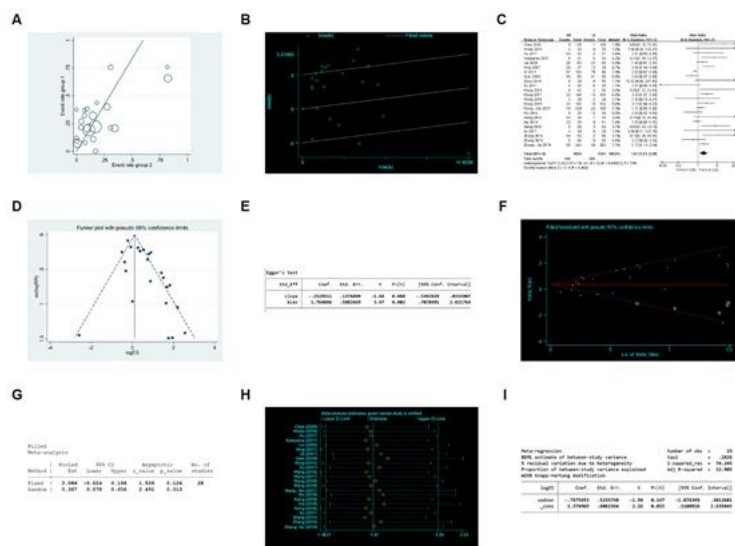


Figure 3

Relationship between lncRNAs expression levels and DM. (A) Labbe graph for heterogeneity. (B) Galbraith plot for heterogeneity. (C) The forest plot of the relationship between lncRNAs expression levels and DM for RCC. (D) The publication bias qualitative analysis of the eligible studies with DM via Begg's test. (E) The publication bias quantitative analysis of the eligible studies with DM via Begg's test. (F) Trim and fill qualitative analysis of the eligible studies with DM. (G) Trim and fill quantitative analysis of the eligible studies with DM. (H) The sensitivity analysis of the eligible studies with DM. (I) The meta regression of the eligible studies with DM.

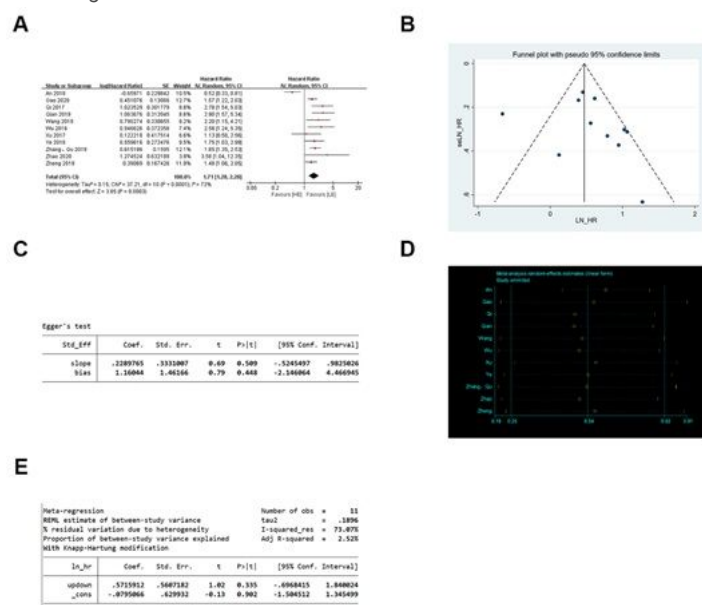


Figure 4

Relationship between lncRNAs expression levels and prognosis. (A) The forest plot of the association between lncRNAs expression levels and prognosis (OS). (B) The publication bias qualitative analysis of the eligible studies with prognosis (OS) via Begg's test. (C) The publication bias quantitative analysis of the eligible studies with prognosis (OS) via Begg's test. (D) The sensitivity analysis of the eligible studies with prognosis (OS). (E) The Meta Regression of the eligible studies with prognosis (OS).