Circular RNAs Serve as Prognostic, Diagnostic and Clinicopathological Markers in Lung Cancer: An Updated Systematic Review and Meta-Analysis

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Abstract

Background: In recent years, the roles of circular RNAs (circRNAs) in the biogenesis and clinical application have gradually garnered much interest in the field of cancer research. However, high-quality studies evaluating the roles of circRNAs in clinicopathological features and clinical application of lung cancer are still unrevealed. Herein, we aimed to elucidate the functions of circRNAs in the association with clinicopathology, diagnosis and prognosis in lung cancer.

Methods: Comprehensive and reasonable search strategies were used in four databases up to Nov. 24th, 2019. The odds ratio (*OR*) was used to analyze the risks of circRNAs in lung cancer. Sensitivity (*Sen*), specificity (*Spe*) and area under curve (*AUC*) were used to assess the diagnostic value. What's more, the hazard ratio (*HR*) was used for the analysis of survival outcomes. A fixed-effect model was firstly used in data analysis. If $I^2 > 50\%$ in heterogeneity, the random-effect model was chosen.

Results: A total of 50 studies with 3815 samples were incorporated into our meta-analysis, in which 40 focused on clinical characteristics, 10 related to diagnosis and 31 were aimed at prognosis. In terms of clinical characteristics, both *OR* and 95% confidence interval (*95%CI*) were shown that circRNAs were significantly associated with TNM, tumor differentiation, lymph node metastasis, distal metastasis and tumor size in lung cancer. For diagnosis, both upregulated and downregulated circRNAs distinguished patients with lung cancer from healthy people with pooled *Sen*, *Spe* and *AUC*, of which the values were 0.78, 0.76 and 0.81 respectively. In the section of prognosis, circRNAs can better predict the survival time of patients with lung cancer (overall survival, OS: *HR*=0.46, *95%CI*: 0.33–0.65 in downregulated circRNAs; *HR*=2.23, *95%CI*: 1.97-2.53 in upregulated circRNAs).

Conclusions: The results presented here suggested that circRNAs were the potential cancer biomarkers in clinicopathology, diagnosis and prognosis of lung cancer patients, which deserve further application in clinical practice.

Background

According to global cancer statistics in 2018, lung cancer has become the leading cause of cancer morbidity and mortality, with 11.6% of all new diagnosis cancer cases and 18.4% of total cancer death cases[1]. Lung cancer is composed of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), of which NSCLC accounts for nearly 85%. Complete surgical resection is the most effective and available treatment in the early-stage of lung cancer. Notably, 5-year survival rates of lung cancer will decrease by 45% in stage III, compared with stage I of lung cancer[2]. However, due to a lack of accurate and sensitive screening methods to detect early-stage lung cancer, it was estimated that 7 out of 10 patients died after the diagnosis of lung cancer in the United States[3]. Hence, it is urgent to seek and develop brand-new biomarkers to improve the status.

Circular RNA (circRNA), a loop structure with a 3'-5' covalently closed link, is a novel molecule for tumorigenesis and tumor development[3]. Since the absence of 5'-cap structure and 3'-poly(A) tail, circRNAs are stable and kept from exonucleases[4]. Characterized by master regulatory function, circRNAs has become the focus of attention in the research of lung cancer. In recent years, researches on circRNAs on oncogenesis, metastasis, diagnosis and prognosis have been extensively performed in various cancer types, especially in lung cancer. Xin Huang et al. pooled a total of 23 studies to assess the relationship between circRNAs and lung cancer in terms of clinicopathological features, prognosis and diagnosis[5]. However, the results showed in their study were lack of convincing due to limited included researches.

Although a growing body of studies suggested that circRNAs play a key role in lung cancer in the fields of diagnosis, prognosis and treatment, a high-quality study with reliable pooled results is still absent. Therefore, our study shed highlight on investigating and assessing the diagnostic and prognostic roles of circRNAs in lung cancer. What's more, the

relationship between clinicopathological features in lung cancer and circRNAs was also thoroughly evaluated in this study.

Methods

Search strategy

The searching work was performed in four main databases, including PubMed, PubMed Central (PMC), Embase and Web of Science, up to Nov. 24th, 2019, with a search strategy combining terms: (“circRNA” or “circular RNA”) and (“lung cancer” or “lung neoplasm” or “lung carcinoma” or “lung tumor”) in Title/Abstract and Subject heading. The references of the final searched studies were initially processed examination by title and abstract, and then potential eligible studies were further looked for full-text articles when necessary. It is indispensable for two researchers (Liang and Guo) to independently carry out this part.

Data inclusion and exclusion

Studies included in our work must meet the following criteria:

- Studies focused on the relationship between certain circRNA and lung cancer and data included clinicopathology, diagnosis or prognosis;
- The total number of the sample (including lung tumor tissue and paired adjacent non-tumorous tissue), Sen, Spe, AUC, *HR* and follow-up time were available;
- Case-control or cohort.
- Researches on circRNA in all kinds of specimens in patients suffering from lung cancer using qRT-PCR were included.

Exclusion can be performed at the following criteria:

- Meta-analysis, review, case report or only abstract;
- The article was not written in English;
- No available data can be extracted in clinical parameters, diagnosis or prognosis;
- Animal researches or cancer cell experiments.

Data extraction

The extracted information was obtained in each eligible study by two independent researchers. To rule out discrepancy and obtain consistent data, extracted information was then cross-checked between the two researchers. Disagreement was solved by consulting with a third researcher (Chen). All collected studies were extracted the following data: first author, publication year, circRNAs, the expression level of circRNA (upregulated or downregulated) and cancer types. For clinicopathological features, the extraction of age, gender, smoking, histological type, tumor size, distal metastasis, lymph node metastasis, differentiation and TNM stage were available. For the part of the diagnosis, the samples of case and control, sample types and diagnostic value, including sensitivity, specificity and AUC were available collected. As for the assessment of prognosis, case number classified by expression level, *HR* and *95%CI*, following-up period, and overall survival (OS) were available obtained. Notably, some of the eligible articles missed the important values (*HR* and *95%CI*), but these values could be calculated by Engauge Digitizer Software (version 11.1). The quality of the articles was examined by the Newcastle-Ottawa scale (NOS, **SupplementaryTable 1**). The articles with scores ≥ 7 were identified as high quality.

Statically analysis

Stata, V14.0 software was utilized to analyze in our meta-analysis to combine Sen, Spe, AUC, *HR* and *OR* value. *OR* and *95%CI* were used to assess clinicopathological features, and sensitivity, specificity and AUC were used to assess the effect of diagnosis. What's more, *HR* and *95%CI* were needed to determine the prediction of prognosis. *Q*-test and I^2 -test were used to determine the heterogeneity between studies. A fixed-effects model was applied for the analysis if $I^2 < 50\%$. The random-effects model would be used otherwise. If $P < 0.1$ in the *Q*-test or $I^2 > 50\%$, sensitivity analysis and subgroup analysis would be performed to further analyze the potential source of heterogeneity. Both Begg's test and Egger's test were used to quantitatively confirm whether publication bias existed. $P < 0.05$ in both results indicated that there was no publication bias in the analysis.

Results

Search results

Referencing comprehensive and appropriate search strategies, the flow chart showed the steps related to screening the studies for the meta-analysis (**Figure 1**). A total of 479 eligible articles were selected from four main databases up to Nov. 24th, 2019. In these articles, 429 records were eliminated, including 232 records for duplicates, 161 records excluded after screening for title and abstract, and 36 studies were got rid of our meta-analysis because of the following reasons: no full-text articles, review or meta-analysis, insufficient data and not related to circRNAs or lung cancer. Finally, 50 full-text articles with a total of 3815 samples acceded to our meta-analysis, including 39 tumor promoters and 15 tumor suppressors. These studies illuminated the correlation between circRNAs and clinical characteristics, diagnosis and prognosis respectively.

Clinical pathology

40 studies with 32 tumor promoters and 8 tumor suppressors included in this part were shown in **Supplementary Table 2-10**. The association between circRNAs expression and clinical characteristics of lung cancer patients was presented in the summary table (**Table 1**). The results indicated that oncogenic circRNAs were remarkably associated with later TMN stage ($OR = 2.74$, *95% CI*: 1.81–4.15), poor differentiation ($OR = 2.22$, *95% CI*: 1.73–2.85), higher rate of lymph node metastasis ($OR = 1.92$, *95% CI*: 1.27–2.90), higher rate of distal metastasis ($OR = 2.86$, *95% CI*: 1.29–6.30) and larger tumor size ($OR = 1.72$, *95% CI*: 1.08–2.46). Oddly enough, upregulated circRNAs had no statistical relationship to TMN stage when compared stage II–VI with stage I. The *P*-value was greater than 0.05 in subgroups analysis of various tumor size. Moreover, the higher expression of downregulated circRNAs was associated with earlier TMN stage ($OR = 0.41$, *95% CI*: 0.21–0.80), lower rate of lymph node metastasis ($OR = 0.32$, *95% CI*: 0.17–0.61), and smaller tumor size ($OR = 0.50$, *95% CI*: 0.27–0.94). Whereas, neither tumor promoters nor suppressors mentioned above were correlated with patients' age, gender, smoking and histological type.

Diagnostic analysis of circRNAs

Our meta-analysis presented the pooled results of 10 upregulated and 6 downregulated circRNAs in 10 studies for diagnosis in lung cancer (**Table 2**). This study estimated some indexes as follows: sensitivity (Sen), 0.78 (0.75–0.80); specificity (Spe), 0.76 (0.71–0.79) (**Supplementary Figure 1**); positive likelihood ratio (PLR), 3.20 (2.70–3.80); negative likelihood ratio (NLR), 0.30 (0.25–0.34); and diagnostic odds ratio (DOR), 11.0 (8.0–14.0) (data not shown), respectively. The heterogeneity (I^2) of overall sensitivity and specificity were 19.8% and 47.6%, respectively. Additionally, we drew a summary receiver operator characteristic (SROC) curve for circRNAs and calculated the value of 0.81 AUC (**Figure 2A**).

Fagan's nomogram and likelihood ratio diagram were used to estimate the clinical value of circRNAs' diagnosis. Fagan's diagram presented that the positive probability of precisely diagnosing lung cancer was 76% at the high expression of oncogenic circRNAs or low expression of anti-tumor circRNAs, while the negative probability was only 23% at the normal expression of upregulated and downregulated circRNAs (Figure 2B). As we can see in Figure 2C, nearly all circRNAs located in lower right quadrants, which means no exclusion or confirmation value of circRNAs in lung cancer. To find out the between-study heterogeneity, subgroup analysis and sensitivity analysis were performed to uncover the source of heterogeneity. The subgroup analysis revealed that only the specificity of upregulated circRNAs had remarkable heterogeneity (Figure 3). The sensitivity analysis illustrated that the stability of results by omitting studies one by one and construed the source of heterogeneity (Supplementary Figure 2). The results of sensitivity analysis revealed that the heterogeneity was mainly derived from the study of Xiaoli Zhu (hsa_circ_0013958 in plasma) and the study of Liang Zong (hsa_circ_102231 in tissue). Although the heterogeneity of sensitivity and especially specificity was overwhelmingly decreased after omitting the above studies one by one, the diagnostic value almost stayed unchanged (Supplementary Figure 3). Furthermore, the funnel plot revealed that publication bias might exist in studies (Supplementary Figure 4) and the results were further quantificationally confirmed by Begg's test ($Z=3.38$, $P=0.001$) and Egger's test ($t=3.85$, $P=0.002$).

Prognostic analysis of circRNAs

31 included studies with 26 upregulated circRNAs and 5 downregulated circRNAs were summarized in Table 3. The figure showed that high expression of oncogenic circRNAs significantly related to poor prognosis (OS: $HR = 2.23$, $95\%CI$: 1.97–2.53), and the elevation of anti-tumor circRNAs was associated with longer overall survival (OS:

$HR = 0.46$, $95\%CI$: 0.33–0.65) (Figure 4). Neither tumor promoters nor tumor suppressors could be found heterogeneity between studies ($I^2 = 0.0\%$). No evidence of publication bias for prognosis was found from Begg's test (upregulated circRNAs: $P=0.134$; downregulated circRNAs: $P=0.462$) and Egger's test (upregulated circRNAs: $P=0.095$; downregulated circRNAs: $P=0.434$).

Discussion

The present study mainly focused on investigating the potential clinical role of circRNAs in lung cancer in terms of clinical characteristics, diagnosis and prognosis. Our results could be obtained from a total of 50 articles involving 3815 samples (lung tumor tissues and paired adjacent non-tumor tissues). The previous meta-analysis reported by Xin Huang et al. revealed that the diagnostic value of circRNAs in lung cancer was 0.86 AUC, with 77% sensitivity and 81% specificity. Moreover, they also reported that patients with increased expression of oncogenic circRNAs had poor survival (OS: $HR=3.24$), while patients with elevated anti-tumor circRNAs had longer survival (OS: $HR=0.57$)[5]. However, the results of the present work were different from the previous study. For diagnosis, although the sensitivity of 78% had a little increase, both AUC and specificity were decreased by 5%. A conclusion that circRNAs might not accurately confirm or exclude lung cancer could be drawn from Fagan's diagram and likelihood ratio diagram. To sum up, the current circRNAs had limited clinical diagnostic value. It turned out that the combination with two or more circRNAs rather than a single might improve overall diagnostic value.

As for prognosis, increased oncogenic circRNAs had more than a two-fold increased risk with poor survival. At the same time, elevated anti-tumor circRNAs had a two-fold decreased risk with unfavorable survival. Our results showed that both upregulated and downregulated circRNAs could be identified as good predictors of prognosis. When it comes to clinical features, something interesting was found in subgroup analysis. Although TNM stages, differentiation of tumor and tumor size were remarkably related to upregulated circRNAs, when compared stage II-IV with stage I in TNM, there was no significant relationship between circRNAs (both tumor promoter and suppressor) and TNM stages. These might be

explained that circRNAs were not sensitively expressed in the early-stage of lung cancer, including stage I and stage II. On the whole, compared with the study of Xin Huang, we newly discovered there were significant associations between downregulated circRNAs and differentiation, lymph node metastasis and tumor size. Moreover, we included patients with distal metastasis in our research and concluded that the expression of upregulated circRNAs was positively correlated with more distal metastasis.

The current study still had some deficiencies. The sample limitation of diagnosis analysis was existing. Only 10 studies with 16 circRNAs were pooled in our study, which would lead to unstable results of the diagnosis. In addition, due to insufficient studies of investigating plasma and serum samples, subgroup analysis could not be performed to analyze the diagnostic value of different samples.

In short, although the investigation of circRNAs has made a great stride in recent years, the diagnostic value of circRNAs is still limited. To summarize, circRNAs were good predictors of prognosis in lung cancer, and effective indicators of many clinical parameters, such as TNM stages, differentiation, lymph node metastasis, tumor size and distal metastasis.

Conclusion

It is possible that the circRNAs can be served as prognostic biomarkers and great predictors of clinical pathology for lung cancer. However, it seems that a single circRNA is not suitable as a good diagnostic biomarker for lung cancer. Therefore, future investigation should be required to develop diagnostic value of the combination of two or more circRNAs.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

Z-ZL and CG contributed to the conception and design of this work. Z-ZL, CG and CC were responsible for the acquisition and analysis of the data. PM and M-MZ wrote parts of the manuscript. L-YZ, HL and T-TZ checked the data and revised the manuscript. All authors have read and approved the manuscript.

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Abbreviations

circular RNAs, circRNAs; odds ratio, OR; 95% confidence interval, 95% CI; sensitivity, Sen; specificity, Spe; area under curve, AUC; non-small cell lung cancer, NSCLC; small cell lung cancer, SCLC; overall survival, OS; positive likelihood ratio, PLR; negative likelihood ratio, NLR; diagnostic odds ratio, DOR; summary receiver operator characteristic, SROC; LSCC, lung squamous cell carcinoma; LAC, lung adenocarcinoma; LC, lung cancer.

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Tables

Figures

Table 1. The summary of clinicopathological features of circRNAs in lung cancer.

Clinical characteristics	Tumor promoter			Tumor suppressor		
	<i>OR</i>	<i>95%CI</i>	<i>P-value</i>	<i>OR</i>	<i>95%CI</i>	<i>P-value</i>
TNM	2.74	1.81-4.15	<0.001	0.41	0.21-0.80	0.009
III-IV vs I-II	2.90	1.90-4.42	<0.001	0.32	0.18-0.59	<0.001
II-IV vs I	1.71	0.26-11.38	0.580	1.12	0.53-2.38	0.762
Differentiation	2.22	1.73-2.85	<0.001	1.82	1.05-3.15	0.032
Modulate/poor vs high	2.32	1.77-3.04	<0.001	1.39	0.60-3.21	0.436
Poor vs high/modulate	1.77	0.95-3.32	0.073	2.23	1.08-4.64	0.031
Lymph node metastasis	1.92	1.27-2.90	0.002	0.32	0.17-0.61	0.001
Distal metastasis (M1 vs M0)	2.86	1.29-6.30	0.009	0.89	0.30-2.59	0.826
Tumor size	1.72	1.08-2.46	0.022	0.50	0.27-0.94	0.032
	1.42	0.39-5.20	0.599	—	—	—
	1.51	0.86-2.64	0.154	0.40	0.14-1.13	0.083
	2.27	0.92-5.62	0.076	0.66	0.34-1.27	0.217
Age	0.87	0.73-1.04	0.119	0.77	0.54-1.10	0.157
	1.40	0.65-2.99	0.391	—	—	—
	1.25	0.66-2.38	0.500	—	—	—
	0.84	0.69-1.03	0.095	0.77	0.54-1.10	0.157
	0.70	0.42-1.15	0.160	—	—	—
Gender	0.94	0.78-1.12	0.474	0.94	0.62-1.42	0.760
Smoking	1.03	0.81-1.30	0.836	1.17	0.60-2.30	0.641
Histological type (LSCC vs LAC)	1.12	0.85-1.49	0.424	0.73	0.40-1.31	0.287
Note: LSCC, lung squamous cell carcinoma; LAC, lung adenocarcinoma; <i>OR</i> , odds ratio; <i>CI</i> , confidence interval.						

Table 2. The characteristics of included circRNAs in lung cancer for diagnosis analysis.										
Study	Year	CircRNA	Cancer Type	Sample		Regulation	Sample Type	Diagnosis power		
				Case	Control			SEN	SPE	AUC
Xiaoxia Liu [6]	2019	hsa_circ_0005962	LAC	153	54	Up	Plasma	0.72	0.72	0.73
Lijian Chen [7]	2019	hsa_circ_100146	NSCLC	40	40	Up	Tissue	0.76	0.58	0.64
Jipeng Li [8]	2018	hsa_circ_0079530	NSCLC	92	92	Up	Tissue	0.76	0.72	0.76
Liang Zong [9]	2018	hsa_circ_102231	LAC	57	57	Up	Tissue	0.81	0.89	0.90
Shaoyan Zhang [10]	2018	hsa_circ_0014130	NSCLC	46	46	Up	Tissue	0.87	0.85	0.88
Xiuyuan Li [11]	2018	circ-PVT1	NSCLC	45	45	Up	Tissue	0.83	0.68	0.80
Xiuyuan Li [11]	2018	circ-PVT1	NSCLC	45	45	Up	Serum	0.71	0.80	0.79
Xiaoli Zhu [12]	2017	hsa_circ_0013958	LAC	49	49	Up	Tissue	0.76	0.80	0.82
Xiaoli Zhu [12]	2017	hsa_circ_0013958	LAC	30	30	Up	Plasma	0.67	0.93	0.80
Chunmei Fan [13]	2019	circ-MAN1A2	LC	45	121	Up	Serum	0.51	0.79	0.65
Xiaoxia Liu [6]	2019	hsa_circ_0086414	LAC	153	54	Down	Plasma	0.77	0.67	0.78
Yanni Zhang [14]	2018	circ-FOXO3	NSCLC	45	45	Down	Tissue	0.8	0.73	0.78
Fei Xu	2018	hsa_circ_0072309	LSCC	43	43	Down	Tissue	0.88	0.74	0.87

[15]											
Fei Xu	2018	hsa_circ_0006114	LSCC	43	43	Down	Tissue	0.86	0.72	0.82	
[15]											
Fei Xu	2018	hsa_circ_0006460	LSCC	43	43	Down	Tissue	0.81	0.70	0.78	
[15]											
Fei Xu	2018	hsa_circ_0077837	LSCC	43	43	Down	Tissue	0.86	0.81	0.86	
[15]											
Note: NSCLC, non-small cell lung cancer; LC, lung cancer; LAC, lung adenocarcinoma; LSCC, lung squamous cell carcinoma; SEN, sensitivity; SPE, specificity; AUC, area under curve.

Figure 1

Table 3. The summary of included circRNAs in lung cancer for prognosis.							
Author/Year	circRNA	Up	Cancer type	Expression		<i>HR (95%CI)</i>	Follow-up (months)
		Down		High	Low		
Jingquan Han[16]	circ-BANP	Up	LC	28	31	2.54(0.38-5.68)	60
Liang Zong[9]	has_circRNA_102231	Up	LC	29	28	1.04(0.36-2.97)	60
Mantang Qiu[17]	circPRKCI	Up	LAC	55	34	1.98(1.15-3.58)	90
Yuanshan Yao[18]	has_circ_0001946	Up	LAC	38	34	1.70(0.8-3.62)	60
Bai-Quan Qiu[19]	circ-FGFR3	Up	NSCLC	34	29	2.53(1.16-5.48)	80
Liuxin Wang[20]	circ-VANGL1	Up	NSCLC	49	46	1.66(0.82-3.37)	60
Qi Huang[21]	circ-ATXN7	Up	NSCLC	45	12	1.09(0.48-2.45)	42
Guohua Liu[22]	circ-FOXMI	Up	NSCLC	44	36	2.05(1.24-3.37)	60
Jingchun An[23]	has_circ_0003645	Up	NSCLC	32	27	2.67(1.48-4.81)	60
Wei Han[24]	circ-RAD23B	Up	NSCLC	20	20	1.91(0.70-5.18)	60
Si Qin[25]	circ-PVT1	Up	NSCLC	43	47	1.68(0.65-4.31)	60
You Zhou[26]	hsa_circ_0004015	Up	NSCLC	16	19	1.57(0.37-5.26)	60
B. YAN[27]	ciRS-7	Up	NSCLC	NG		2.03(1.35-3.06)	100
Qinguang Zou[28]	has_circ_0067934	Up	NSCLC	41	38	2.68(1.89-4.00)	80
Yi Qi[29]	hsa_circ_0007534	Up	NSCLC	56	42	2.10(1.29-3.42)	60
Fucheng Zhao[30]	circ-FADS2	Up	NSCLC	22	21	2.77(0.97-7.93)	60
Yongsheng Li[31]	has_circ_0016760	Up	NSCLC	45	38	2.24(1.36-3.69)	60
Wei Liu[32]	hsa_circRNA_103809	Up	NSCLC	44	44	1.29(0.43-3.86)	80
Chongyu Su[33]	ciRS-7	Up	NSCLC	77	55	2.14(1.44-3.20)	60
J. WANG[34]	has_circ_0067934	Up	NSCLC	79	80	3.77(1.50-6.67)	60
Danhua Qu[35]	hsa_circ_0020123	Up	NSCLC	40	40	1.45(0.43-4.79)	80
Xiaofei Zhang[36]	ciRS-7	Up	NSCLC	41	19	3.58(1.69-4.83)	80
Jingru Wan[37]	has_circ_0020123	Up	NSCLC	28	27	2.50(1.35-4.64)	60
X.-Y. LI[38]	hsa_circ_000984	Up	NSCLC	80	75	3.33(1.26-4.45)	60
Lingchi Ding[39]	has_circ_001569	Up	NSCLC	29	27	2.17(1.11-4.26)	60
Xiuyuan Chen[40]	circ-HIPK3	Up	NSCLC	25	51	2.27(0.76-6.85)	60
Liu Yang[41]	hsa_circ_0046264	Down	LC	55	44	0.53(0.27-1.03)	20
Daishi Chen[42]	hsa_circ_100395	Down	LC	35	34	0.44(0.20-1.02)	150
Yuanshan Yao[43]	has_circ_0006427	Down	LAC	54	40	0.44(0.21-0.93)	60
Binbin Zhang[44]	circ-MTO1	Down	LAC	31	32	0.57(0.15-2.21)	100

The flowchart showed the algorithm on how to perform the exclusion and inclusion of the eligible studies in our meta-analysis.

Figure 2

The clinical application of circRNAs in lung cancer. (A) The ability of circRNAs to differentiate patients with lung cancer from normal people was calculated from the Summary receiver operating characteristic (SROC) curve. (B) Fagan's nomogram was shown to estimate the clinical utility of overall circRNAs to differentiate patients with lung cancer from normal people. (C) Likelihood ratio diagram showed the clinical diagnosis value of circRNAs in lung cancer.

Figure 3

Forest plot by subgroup analysis of diagnostic value in the application of circRNAs in lung cancer. (A) Upregulated circRNAs; (B) Downregulated circRNAs.

Figure 4

Forest plot of overall survival for prognosis of circRNAs in lung cancer. (A) Upregulated circRNAs; (B) Downregulated circRNAs.

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