Prognostic and diagnostic value of circRNA expression in colorectal carcinoma: a meta-analysis

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Abstract

Background: Circular RNAs (circRNAs) are new stars in the network of noncoding RNAs and are regarded as key control factors in numerous tumours. The purpose of our study was to evaluate the clinical, prognostic and diagnostic role of circRNAs in colorectal cancer. The quality of all the articles were assessed by the Newcastle-Ottawa Scale.

Methods: An online search in electronic databases, including the PubMed, Cochrane Library and Web of Science online databases, was conducted to identify as many relevant papers as possible. Nineteen relevant studies were enrolled in this meta-analysis, with seven on diagnosis, eight on prognosis and 11 on clinicopathological features.

Results: For the diagnostic value of circRNAs, the pooled results showed that the area under the curve (AUC) was 0.82 for identifying patients with colorectal cancer, with a sensitivity of 83% and a specificity of 72%. In terms of prognosis, carcinogenic circRNAs have a negative effect on overall survival (OS: HR = 2.29, 95% CI: 1.50-3.52), and increases in tumour suppressor circRNA expression are associated with longer survival (OS: HR = 0.37, 95% CI: 0.22-0.64). And the elevated expression of oncogenic circRNAs is associated with poor clinical features while tumor suppressor circRNAs are the complete opposite.

Conclusions: These results suggest that circRNAs may be a potential biomarker for the diagnosis and prognosis of colorectal cancer.

Background

Circular RNAs (circRNAs), consisting of a circular configuration through a typical 5’ to 3’-phosphodiester bonds, are a novel class of endogenous noncoding RNAs[1-3]. CircRNAs play a special role as molecular markers in many human diseases including tumors, due to their conservation, abundance and tissue specificity[4]. In addition, circRNAs can be classified into four categories: exon circRNAs, intron circRNAs, exon-intron circRNAs, and intergenic circRNAs[5]. Different types of circRNAs have distinct functions, including interacting with RNA binding proteins, regulating the stability of the mRNAs, regulating gene transcription, sponging microRNAs and participating in translation[5-7]. However, the underlying mechanisms and functions of circRNAs remain uncertain.

Extensive studies have indicated that circRNAs play a major role in tumourigenesis, the development of cardiovascular diseases, and the pathogenesis of neurodegenerative diseases[8]. However, the differential expression of circRNAs and their definite functions are still not totally clear in human colorectal cancer (CRC). Colorectal cancer is among the most common malignancies of the digestive system and the fourth leading cause of cancer-related death worldwide[9]. Although considerable progress has been made in the diagnosis and treatment of this disease, the prognosis of CRC patients is still poor, due to the delay in early diagnosis and the high frequency of metastasis and recurrence[10]. In this study, we performed a meta-analysis and a comprehensive search of all relevant literature to summarize the diagnostic, prognostic and clinical significance of circRNAs in CRC patients.

Methods

Data search strategy

The PubMed, Cochrane Library, and Web of Science online databases were searched for studies on circRNA research that were published in English before May 15, 2019. The search strategy in this study included the following terms: (1)" circRNA" or "circular RNA" and (2) "colorectal cancer" or "colorectal carcinoma" or "colorectal tumour" or "CRC". Two researchers (Yuan and Guo) assessed the title, abstract and full text to identify the appropriate articles. Other researchers (Li), together with the former two researchers were involved in the data extraction. Any disagreements were settled by a third researcher (Chen). Then, the data were extracted from the selected articles and populated it into a table.

Inclusion and exclusion criteria

This study used the following criteria when selecting articles. Studies that met the following inclusion criteria were included in the meta-analysis: (1) cohort study or case-control study; (2) patients with a pathological diagnosis of CRC; and (3) studies that detected the circRNA expression level and provided information on the clinicopathological features and prognosis of patients. Studies were excluded if the following excluded criteria were met: (1) not about circRNAs or CRC; (2) data similar to that in previous studies; (3) case reports, animal experiments, reviews, and so on; and (4) no applicable data.

Data extraction and quality assessment

Two investigators (Yuan and Guo) evaluated the eligibility of the studies and independently extracted the following data: (a) author, year of publication, circRNA type, cancer type, case number and detection method; (b) expression level of the circRNAs, follow-up time and overall survival (OS); (c) the sensitivity and specificity of the circRNAs for diagnosis; and (d) clinical data with age, gender, tumour size, TNM stage, differentiation, lymphatic metastasis, distal metastasis and so on[11]. The Newcastle-Ottawa Scale (NOS; Supplementary Table S1) was adopted to evaluate the quality of the studies. The quality assessment of each included study was carried out by two independent investigators (Yuan and Guo). A third investigator (Li) discussed any differences. A study was considered high quality if the score was ≧7.

Statistical analysis

Statistical analysis was performed using STATA software (version 14). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to measure the clinicopathological parameters and hazard ratios (HRs) were used to assess the overall survival (OS). The number of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) were calculated and finally the pooled sensitivity, specificity and the area under the ROC curve (AUC) were obtained to assess the diagnostic value of circRNAs. The chi-square test and I^2 statistic were used to evaluate heterogeneity. When the I^2 value was < 50%, no observable heterogeneity was suggested, and a fixed effects model was used [12]; otherwise, a random effects model was utilized. Sensitivity

analysis was used to estimate the potential sources of heterogeneity. Qualitative evaluation of publication bias was conducted through funnel plots, and quantitative evaluation was conducted by Begg and Egger's tests.

Results

Search Results

As shown in Fig. 1, 83 relevant studies were obtained from the database. Among them, 46 were full-text reviews and 27 were abstract reviews. Then, 27 articles were excluded for the following reasons: 5 were not about circRNAs or CRC, 10 did not report relevant outcomes, 3 were review articles, 1 was animal data, and 8 had insufficient data. In summary, there were 19 studies[13-31] included in this study, with a total of 1307 patients, including 11 on clinical parameters, 8 on prognosis and 7 on diagnosis.

Study characteristics

The main features of this analysis are presented in Table 1 and Table 2. All studies were published between 2015 and 2019. The number of samples ranged from 40-204, and the follow-up time of patients ranged from 57 months to 123 months. As shown in Table 1, six circRNAs were identified as tumour promoters, and two circRNAs were identified as tumour suppressors. As shown in Table 2, seven articles with sensitivity, specificity, and AUC data were included for the diagnosis analysis. All studies were of great quality with the quality scores ranging from 7 to 8(Supplementary Table 1).

Clinicopathological parameters

The associations between circRNAs and the clinical features of CRC patients are shown in Table 3. There was a significant correlation between the increase in oncogenic circRNAs expression and poor clinical features：tumor size: OR=1.769, 95% CI: 1.097 -2.852 ; differentiation grade: OR=1.743, 95% CI: 1.032-2.946; TNM stage: OR=3.320, 95% CI: 1.529 -7.207; T classification: OR=3.410, 95% CI :2.088-5.567; lymph node metastasis: OR=3.357, 95% CI: 2.160-5.215; distal metastasis: OR = 4.338, 95% CI: 2.503-7.520).In addition, high expression of tumor-suppressor circRNAs were related to favorable clinical parameter (differentiation grade: OR=0.453 , 95%CI : 0.261-0.787; T classification: OR=0.553, 95%CI: 0.328-0.934; distal metastasis: OR =0.196, 95%CI: 0.077 -0.498). However, no notable differences were found in terms of age, gender, or tumor location.

Overall survival

As shown in Fig.2A, the elevated expression of oncogenic circRNAs was notably associated with a poor prognosis (OS: HR = 2.29, 95% CI: 1.50–3.52, p < 0.001), and a fixed-effects model was used with no great heterogeneity (I^2 = 0.0%, p = 0.937). In addition, the low expression of tumour-suppressor circRNAs was related to shorter survival times (OS: HR = 0.37, 95% CI: 0.22–0.64, p < 0.001). No great heterogeneity (I^2 = 0.0%, p = 0.525) was found, and a fixed-effects model was employed (Fig. 2B).

Diagnosis analysis

Fig. 3 provides the forest plot of the sensitivity and specificity of circRNAs. And the random-effects model was employed with high heterogeneity (I^2 = 76.15% and I^2=48.29%). The pooled results showed a sensitivity of 0.83 (95% CI: 0.75-0.88) and a specificity of 0.72 (95% CI: 0.66-0.78). In addition, the summary receiver operator characteristic (SROC) curve (Fig. 4) was calculated and AUC was 0.82 (95% CI 0.78–0.85). Taken together, these results suggest that circRNAs have a good diagnostic accuracy for CRC.

Publication bias and sensitivity analysis

From the funnel plot, there was no evidence of publication bias in our study (Supplementary Figure 1). There was no obvious publication bias according to Begg's funnel plot (p = 0.213; Supplementary Figure 2) and Egger's test (p = 0.722; Supplementary Figure 3). The sensitivity analysis suggested that the results were not altered greatly when omitting studies one by one (Supplementary Figure 4). Furthermore, Deek's funnel plot asymmetry test[32] showed no obvious publication bias(p=0.07) for the diagnosis analysis (Supplementary Figure 5).

Discussion

Recently, many studies have focused on the significant role of circRNAs, whereas no relevant meta-analyses on circRNA expression in CRC have been performed. A total of 1307 cancer patients from nineteen eligible studies were collected and analysed in this study, including seven on diagnosis, eight on prognosis, and eleven on clinicopathological features. For clinical features, the high expression of oncogenic circRNAs was notably associated with worse clinical parameters, while tumour-suppress circRNAs showed the opposite associations. For prognostic value, higher expression levels of oncogenic circRNAs indicated a poor survival, while higher expression levels of tumour suppressor circRNAs indicated the opposite. In addition, the summarized results showed AUC of 0.82, with 83% sensitivity and 72% specificity for the diagnostic value of circRNAs in CRC patients.

Our current study observed a significant relationship between abnormal circRNA expression and its diagnostic value in CRC patients. Since the tumour tissues, plasma, and even cells from patients with aberrant expression of circRNAs can be easily detected, measurements can be performed conveniently and economically. Coupled with the structural stability of circRNAs, circRNAs are a promising biomarker in the diagnosis of CRC. Although sensitivity analysis showed no significant heterogeneity, more pertinent investigations are warranted to corroborate our findings.

In previous meta-analyses, only five meta-analyses[33-37] detected an association between the circRNAs and carcinoma. However, in the studies of Wang et al[33], Chen et al[34] and Li et al[35], only one study was included to investigate the relationship between the circRNAs and CRC. Li et al[36] and Ding et al[37] assessed the diagnostic value of circRNAs for human cancers, in which five articles were included to investigate the diagnostic value of circRNAs in CRC, whereas they failed to discuss the role of circRNAs in CRC patients. In the

present study, we collected all the relevant articles published to date and performed a meta-analysis including nineteen articles with 1307 CRC patients. Furthermore, we detected the prognostic and diagnostic value of circRNA expression in CRC patients. Nonetheless, further large-scale studies are needed to confirm these results.

However, several limitations must be considered when interpreting the conclusions of this meta-analysis. First, since all patients included in the article were from China, this reduced the applicability of the results across different ethnicities and regions. Moreover, there was a limited number of articles for a subgroup analysis according to different circRNAs. Furthermore, a relatively small number of patients was included in this meta-analysis, so larger-scale studies would be necessary to verify the obtained results. Finally, several studies did not provide HRs with their 95% CIs in the article, so we needed to extract them from the Kaplan-Meier survival curve.

Conclusion

In summary, our study demonstrated a crucial relationship between the variant expression of circRNAs and the diagnosis, prognosis clinicopathological features in patients with CRC. Furthermore, circRNAs may be novel biomarkers and therapeutic targets for colorectal cancer.

Abbreviations

OR: odds ratios; 95% CI: 95% confidence interval; HR: Hazard ratio; OS: Overall survival; circRNAs: circular RNAs; CRC: colorectal cancer; SROC: the summary receiver operator characteristic curve; AUC: the area under the curve.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data analyzed during this study are included in this published article.

Competing interests

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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None.

Authors' contributions

Conceived and designed the experiments: JTC and XXL. Performed the experiments: JPY, DMG, XXL, CZZ and JTC. Analyzed the data: JPY and DMG. Contributed analysis tools/materials: JPY, DMG, XXL and JTC. Wrote the paper: JPY and DMG. All authors have read and approved the final manuscript.

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References

1. Hentze MW, Preiss T: **Circular RNAs: splicing's enigma variations**. *EMBO J* 2013, **32**(7):923-925.
2. Chen LL, Yang L: **Regulation of circRNA biogenesis**. *RNA Biol* 2015, **12**(4):381-388.
3. Starke S, Jost I, Rossbach O, Schneider T, Schreiner S, Hung LH, Bindereif A: **Exon circularization requires canonical splice signals**. *Cell Rep* 2015, **10**(1):103-111.
4. Meng S, Zhou H, Feng Z, Xu Z, Tang Y, Li P, Wu M: **CircRNA: functions and properties of a novel potential biomarker for cancer**. *Mol Cancer* 2017, **16**(1):94.
5. Wilusz JE, Sharp PA: **Molecular biology. A circuitous route to noncoding RNA**. *Science* 2013, **340**(6131):440-441.
6. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M *et al*: **Circular RNAs are a large class of animal RNAs with regulatory potency**. *Nature* 2013, **495**(7441):333-338.
7. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J: **Natural RNA circles function as efficient microRNA sponges**. *Nature* 2013, **495**(7441):384-388.
8. Zhao Y, Alexandrov PN, Jaber V, Lukiw WJ: **Deficiency in the Ubiquitin Conjugating Enzyme UBE2A in Alzheimer's Disease (AD) is Linked to Deficits in a Natural Circular miRNA-7 Sponge (circRNA; ciRS-7)**. *Genes (Basel)* 2016, **7**(12).
9. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A: **Colorectal cancer statistics, 2017**. *CA Cancer J Clin* 2017, **67**(3):177-193.
10. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J: **Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer**. *Nat Rev Cancer* 2017, **17**(4):268.
11. Huang X, Zhang W, Shao Z: **Prognostic and diagnostic significance of circRNAs expression in lung cancer**. *J Cell Physiol* 2019, **234**(10):18459-18465.
12. Egger M, Davey Smith G, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test**. *BMJ* 1997, **315**(7109):629-634.
13. Fang G, Ye BL, Hu BR, Ruan XJ, Shi YX: **CircRNA_100290 promotes colorectal cancer progression through miR-516b-induced downregulation of FZD4 expression and Wnt/beta-catenin signaling**. *Biochem Biophys Res Commun* 2018, **504**(1):184-189.

14. Guo JN, Li J, Zhu CL, Feng WT, Shao JX, Wan L, Huang MD, He JD: **Comprehensive profile of differentially expressed circular RNAs reveals that hsa_circ_0000069 is upregulated and promotes cell proliferation, migration, and invasion in colorectal cancer**. *Onco Targets Ther* 2016, **9**:7451-7458.
15. Ji W, Qiu C, Wang M, Mao N, Wu S, Dai Y: **Hsa_circ_0001649: A circular RNA and potential novel biomarker for colorectal cancer**. *Biochem Biophys Res Commun* 2018, **497**(1):122-126.
16. Jin C, Wang A, Liu L, Wang G, Li G: **Hsa_circ_0136666 promotes the proliferation and invasion of colorectal cancer through miR-136/SH2B1 axis**. *J Cell Physiol* 2019, **234**(5):7247-7256.
17. Li J, Ni S, Zhou C, Ye M: **The expression profile and clinical application potential of hsa_circ_0000711 in colorectal cancer**. *Cancer Manag Res* 2018, **10**:2777-2784.
18. Li X, Wang J, Zhang C, Lin C, Zhang J, Zhang W, Zhang W, Lu Y, Zheng L, Li X: **Circular RNA circITGA7 inhibits colorectal cancer growth and metastasis by modulating the Ras pathway and upregulating transcription of its host gene ITGA7**. *J Pathol* 2018, **246**(2):166-179.
19. Li XN, Wang ZJ, Ye CX, Zhao BC, Huang XX, Yang L: **Circular RNA circVAPA is up-regulated and exerts oncogenic properties by sponging miR-101 in colorectal cancer**. *Biomed Pharmacother* 2019, **112**:108611.
20. Li XN, Wang ZJ, Ye CX, Zhao BC, Li ZL, Yang Y: **RNA sequencing reveals the expression profiles of circRNA and indicates that circDDX17 acts as a tumor suppressor in colorectal cancer**. *J Exp Clin Cancer Res* 2018, **37**(1):325.
21. Ruan H, Deng X, Dong L, Yang D, Xu Y, Peng H, Guan M: **Circular RNA circ_0002138 is down-regulated and suppresses cell proliferation in colorectal cancer**. *Biomed Pharmacother* 2019, **111**:1022-1028.
22. Wang F, Wang J, Cao X, Xu L, Chen L: **Hsa_circ_0014717 is downregulated in colorectal cancer and inhibits tumor growth by promoting p16 expression**. *Biomed Pharmacother* 2018, **98**:775-782.
23. Wang J, Li X, Lu L, He L, Hu H, Xu Z: **Circular RNA hsa_circ_0000567 can be used as a promising diagnostic biomarker for human colorectal cancer**. *J Clin Lab Anal* 2018, **32**(5):e22379.
24. Wang Z, Su M, Xiang B, Zhao K, Qin B: **Circular RNA PVT1 promotes metastasis via miR-145 sponging in CRC**. *Biochem Biophys Res Commun* 2019, **512**(4):716-722.
25. Yong W, Zhuoqi X, Baocheng W, Dongsheng Z, Chuan Z, Yueming S: **Hsa_circ_0071589 promotes carcinogenesis via the miR-600/EZH2 axis in colorectal cancer**. *Biomed Pharmacother* 2018, **102**:1188-1194.
26. Zeng K, Chen X, Xu M, Liu X, Hu X, Xu T, Sun H, Pan Y, He B, Wang S: **CircHIPK3 promotes colorectal cancer growth and metastasis by sponging miR-7**. *Cell Death Dis* 2018, **9**(4):417.
27. Zhuo F, Lin H, Chen Z, Huang Z, Hu J: **The expression profile and clinical significance of circRNA0003906 in colorectal cancer**. *Onco Targets Ther* 2017, **10**:5187-5193.
28. Zhang R, Xu J, Zhao J, Wang X: **Silencing of hsa_circ_0007534 suppresses proliferation and induces apoptosis in colorectal cancer cells**. *Eur Rev Med Pharmacol Sci* 2018, **22**(1):118-126.
29. Xie H, Ren X, Xin S, Lan X, Lu G, Lin Y, Yang S, Zeng Z, Liao W, Ding YQ *et al*: **Emerging roles of circRNA_001569 targeting miR-145 in the proliferation and invasion of colorectal cancer**. *Oncotarget* 2016, **7**(18):26680-26691.
30. Weng W, Wei Q, Toden S, Yoshida K, Nagasaka T, Fujiwara T, Cai S, Qin H, Ma Y, Goel A: **Circular RNA ciRS-7-A Promising Prognostic Biomarker and a Potential Therapeutic Target in Colorectal Cancer**. *Clin Cancer*

Res 2017, **23**(14):3918-3928.

31. Wang X, Zhang Y, Huang L, Zhang J, Pan F, Li B, Yan Y, Jia B, Liu H, Li S *et al*: **Decreased expression of hsa_circ_001988 in colorectal cancer and its clinical significances**. *Int J Clin Exp Pathol* 2015, **8**(12):16020-16025.
32. Deeks JJ, Macaskill P, Irwig L: **The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed**. *J Clin Epidemiol* 2005, **58**(9):882-893.
33. Wang M, Yang Y, Xu J, Bai W, Ren X, Wu H: **CircRNAs as biomarkers of cancer: a meta-analysis**. *BMC Cancer* 2018, **18**(1):303.
34. Chen Z, Zhang L, Han G, Zuo X, Zhang Y, Zhu Q, Wu J, Wang X: **A Meta-Analysis of the Diagnostic Accuracy of Circular RNAs in Digestive System Malignancy**. *Cell Physiol Biochem* 2018, **45**(3):962-972.
35. Li J, Li H, Lv X, Yang Z, Gao M, Bi Y, Zhang Z, Wang S, Cui Z, Zhou B *et al*: **Diagnostic performance of circular RNAs in human cancers: A systematic review and meta-analysis**. *Mol Genet Genomic Med* 2019, **7**(7):e00749.
36. Li Y, Zeng X, He J, Gui Y, Zhao S, Chen H, Sun Q, Jia N, Yuan H: **Circular RNA as a biomarker for cancer: A systematic meta-analysis**. *Oncol Lett* 2018, **16**(3):4078-4084.
37. Ding HX, Lv Z, Yuan Y, Xu Q: **The expression of circRNAs as a promising biomarker in the diagnosis and prognosis of human cancers: a systematic review and meta-analysis**. *Oncotarget* 2018, **9**(14):11824-11836.

Tables

TABLE1 Main characteristics of studies for prognosis analysis.

				circRNA expression				
Study	Year	CircRNA	Cancer Type	High	Low	Detection Method	Regulation	Follow-up (months)
Zeng et al.	2018	circHIPK3	CRC	89	89	qRT-PCR	Upregulated	91
Fang et al.	2018	circ_100290	CRC	24	20	qRT-PCR	Upregulated	59
Weng et al.	2017	circCiRS7	CRC	89	76	qRT-PCR	Upregulated	123
Wang et al.	2019	circPVT1	CRC	32	32	qRT-PCR	Upregulated	58
Jin et al.	2018	circ_0136666	CRC	26	26	qRT-PCR	Upregulated	60
Wang et al.	2018	circ_0071589	CRC	20	20	qRT-PCR	Upregulated	58
Li et al.	2018	circ_0000711	CRC	50	51	qRT-PCR	Downregulated	60
Wang et al.	2018	circ_0014717	CRC	23	23	qRT-PCR	Downregulated	57

Note: CRC: colorectal cancer; qRT-PCR: quantitative real time polymerase chain reaction.

TABLE2 Main characteristics of studies for diagnosis analysis.

				Sample size				Diagnosis power		
Study	Year	CircRNA	Cancer Type	case	control	Method	Regulation	Sen.	Spe.	AUC.
Ji et al.	2018	circ_0001649	CRC	64	64	qRT-PCR	downregulated	0.828	0.781	0.857
Li et al.	2018	circITGA7	CRC	69	48	qRT-PCR	downregulated	0.928	0.667	0.879
Wang et al.	2017	circ_0000567	CRC	102	102	qRT-PCR	downregulated	0.833	0.765	0.865
Zhuo et al.	2017	circ_0003906	CRC	122	40	qRT-PCR	downregulated	0.803	0.725	0.818
Ruan et al.	2019	circ_0002138	CRC	35	35	qRT-PCR	downregulated	0.629	0.743	0.725
Wang et al.	2015	circ_001988	CRC	31	31	qRT-PCR	downregulated	0.68	0.730	0.788
Li et al.	2018	circ_0000711	CRC	101	101	qRT-PCR	downregulated	0.910	0.58	0.810

Note: AUC: area under the ROC curve; qRT-PCR: quantitative real-time polymerase chain reaction; Sen: sensitivity; Spe.: specificity; CRC: colorectal cancer.

TABLE 3 Clinical Parameters of circRNAs in CRC.

	Tumor promoter			Tumor Suppressor		
	OR	95%CI	P	OR	95%CI	P
ge (older/younger)	1.078	0.737-1.577	0.698	0.589	0.241-1.437	0.224
ender (M/W)	1.114	0.757-1.639	0.968	0.805	0.491-1.320	0.390
umor size (larger/smaller)	1.769	1.097-2.852	0.019	0.658	0.382-1.132	0.131
umor location (rectum/colon)	0.888	0.572-1.380	0.598	0.902	0.480-1.694	0.748
ifferentiation grade oor/well & moderate)	1.743	1.032-2.946	0.038	0.453	0.261-0.787	0.005
NM stage (III+IV/I+II)	3.320	1.529-7.207	0.002	0.442	0.187-1.042	0.062
classification (T3+T4/T1+T2)	3.410	2.088-5.567	0.000	0.533	0.328-0.934	0.027
ymph node metastasis (Y/N)	3.357	2.160-5.215	0.000	0.389	0.116-1.307	0.127
istant metastasis (Y/N)	4.338	2.503-7.520	0.000	0.196	0.077-0.498	0.001

Note: CI: confidence interval; M: men; N: no; W: women; Y: yes; OR: odds ratio. The results are in bold if p < 0.05.

Figures

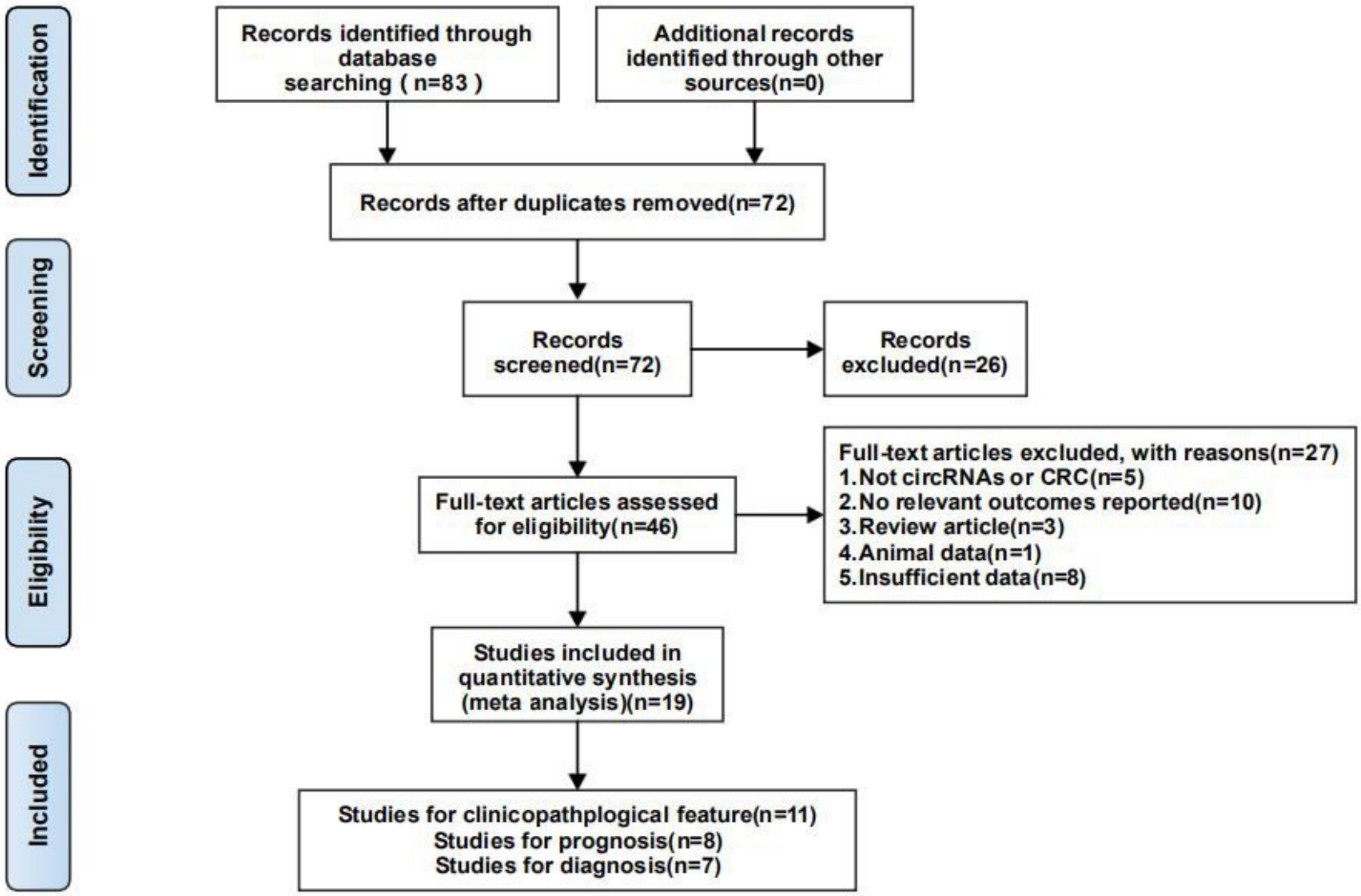

Figure 1

Flowchart of the study selection process

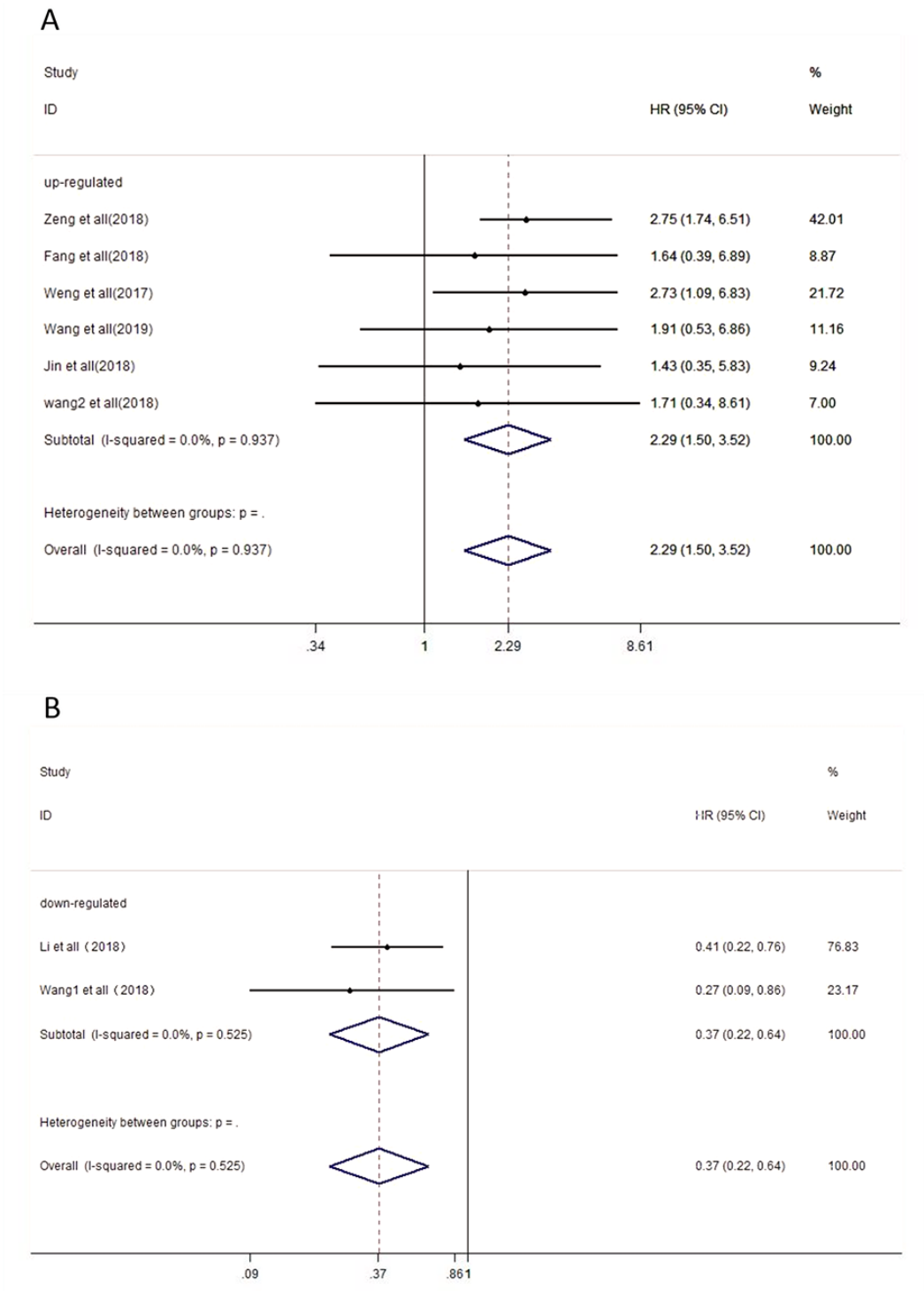

Figure 2

Forest plots for overall survival (OS) according to the type of oncogenic circRNAs(A) and tumor suppressor circRNAs(B) in patients with colorectal cancer (CRC).

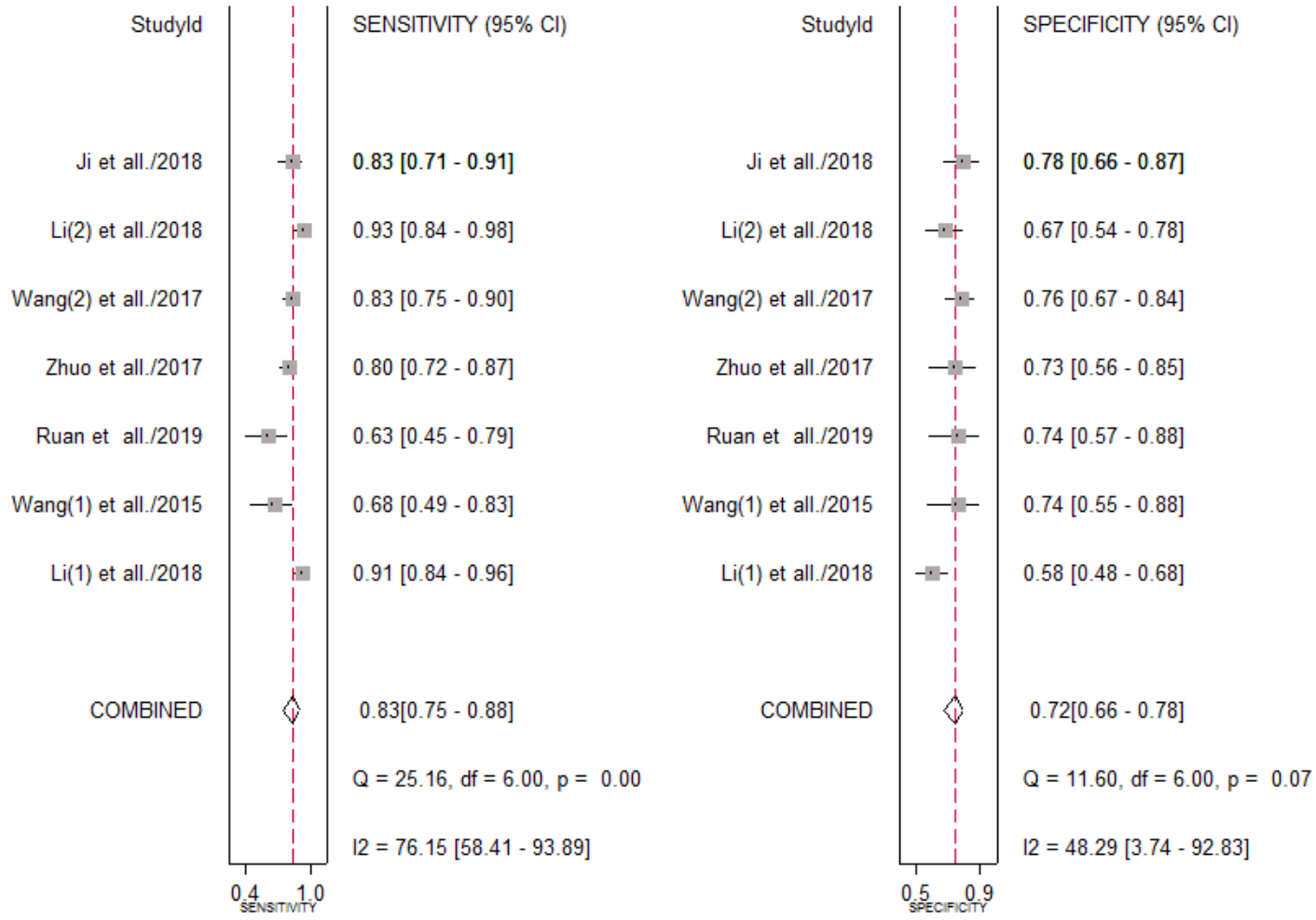

Figure 3

Forest plot of sensitivity and specificity of circRNAs for the diagnosis of colorectal cancer (CRC).

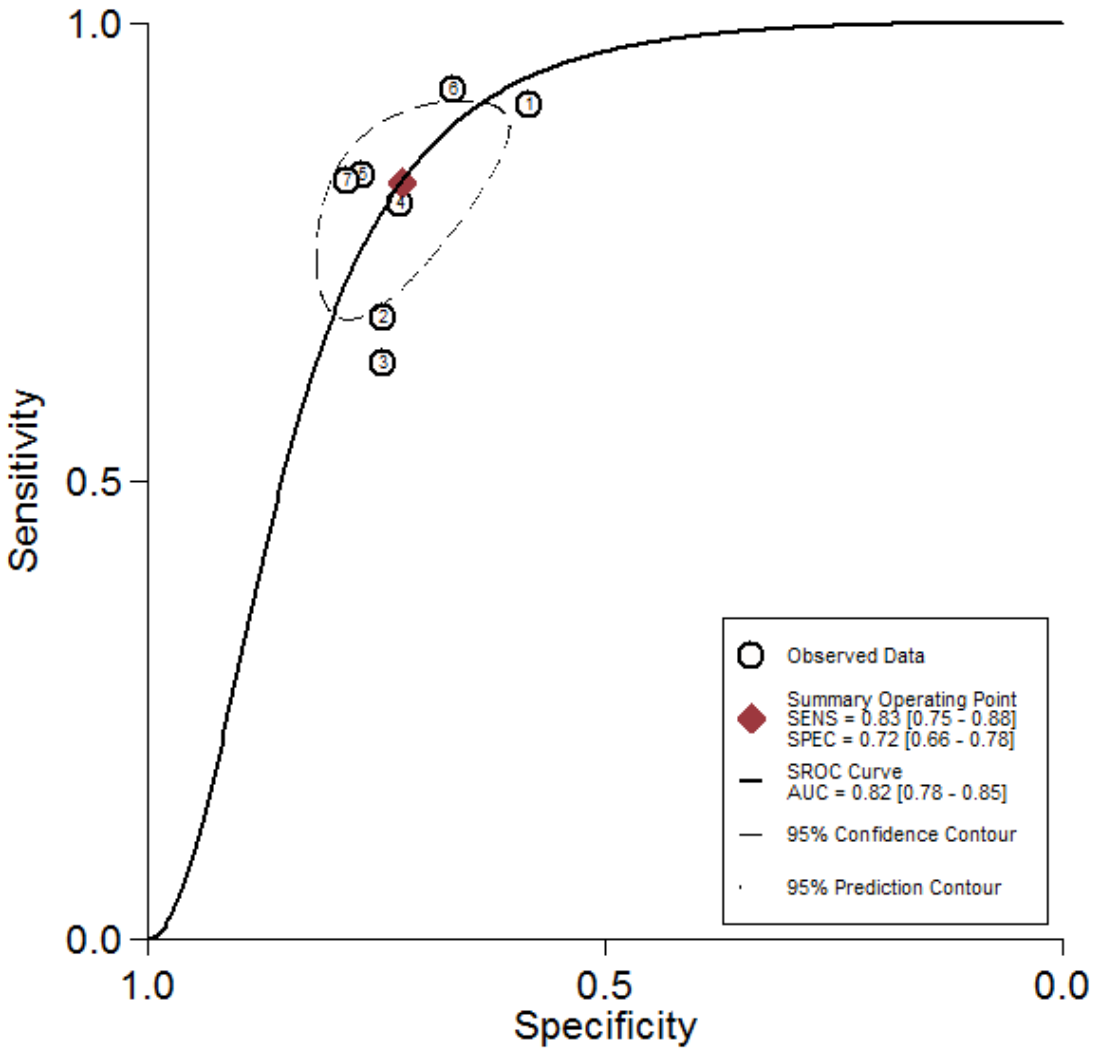

Figure 4

The summary receiver operator characteristic (SROC) curve.

Supplementary Files

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