

## Original Article

# The diagnostic accuracy of circular RNAs in colorectal cancer: a meta-analysis

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**Abstract:** Circular RNAs (circRNAs) have been widely expressed in multiple types of cancer. Nevertheless, there have been limited systematic studies about the diagnostic accuracy of circRNAs in colorectal cancer (CRC). Hence, we attempted to explore the mechanism of circRNAs as diagnostic biomarkers in CRC. Investigation of the PubMed database and other search engines were carried out to identify related literature from 2015 to December 2018. The program of Quality Assessment of Diagnostic Accuracies Studies 2 (QUADAS-2) was used for assessing the study quality. The STATA version 14 (Stata Corporation, College Station, TX, USA) and RevMan5.3 (Cochrane Collaboration, Copenhagen, Denmark) were applied to meta-analysis. There were six studies included in the meta-analysis. The pooled sensitivity and specificity with 95% confidential intervals (95% CIs) were 0.85 (0.78-0.89) and 0.72 (0.65-0.78), respectively. The positive likelihood ratios (PLR) and negative likelihood ratios (NLR) with 95% confidential intervals (95% CIs) were 2.99 (2.43-3.68) and 0.21 (0.16-0.29), respectively. The diagnostic odds ratio (DOR) with 95% confidential interval (95% CI) was 13.95 (9.75-19.97). The overall area under the curve (AUC) value was 0.84, indicating the circRNAs might be diagnostic indicators in colorectal cancer.

**Keywords:** Circular RNA, colorectal cancer, biomarker

## Introduction

Colorectal cancer (CRC) is a common malignancy all over the world [1-3]. Accumulating evidence shows that most patients are in advanced stages of tumor progression when first diagnosed [3], resulting in poor prognosis and raising cancer mortality in the developed world [2-4]. Thus, it is indispensable to seek effective diagnostic markers for CRC patients.

Recently, increasingly more research indicates that circular RNAs are closely linked to many serious diseases, especially cancers [5-7]. As a novel type of endogenous non-coding RNAs (ncRNAs), covalently closed circular RNA molecules (circRNAs), have stable and highly conserved structure [8-12]. In addition, circular RNAs contain multiple miRNA response elements (MREs) which can combine with miRNA to modulate target gene expression levels [13-16]. In recent years, increasing evidence has suggested the crucial role of circRNAs in colorectal cancer [1, 10, 17-28]. Last but not least, there have been limited systematic stud-

ies about the diagnostic accuracy of circRNAs in colorectal cancer (CRC) [29-31]. The association between circRNAs and colorectal cancer remains unclear and is in need of investigation.

In this study, we carried out a meta-analysis summarizing all the circRNAs to seek out the potential function of circRNAs as diagnostic biomarkers in human CRC.

## Material and methods

### Search strategy

The database of Pubmed and other search engines were used for searching the relevant studies published in English until December 24, 2018. The following terms were used in the search: ("circular RNA" or "circRNA") and ("colon cancer" or "colorectal cancer" or "colon tumor"). The eligible studies were manually checked. Two individuals participated in data extraction independently. Disagreement was solved by a third party.

## Selection criteria

Inclusion studies complied with the following criteria: (1) association between circRNAs and colorectal cancer was evaluated; (2) the total number of samples, sensitivity, specificity, and area under the curve (AUC) were available (or can be inferred by the study); (3) the colorectal cancer tissues and adjacent or normal tissues were used in the study as experimental and matched control groups, with information available; (4) study specimen (in tissue) was obtained.

Exclusion studies included: (1) the subject was not from human samples (2) there were no English articles; (3) repeating studies.

## Data extraction and quality assessment

For the eligible literature, two investigators independently collected the following parameters: the first author, quantitative method, publication year, circRNAs name, sample size, sensitivity, specificity, AUC. The program of Quality Assessment of Diagnostic Accuracies Studies 2 (QUADAS-2) was used for assessing the study quality [32].

## Statistical analysis

The software STATA version 14 (Stata Corporation, College Station, TX, USA) and RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark) were used to perform all the statistical analyses. The sensitivity, specificity, diagnostic odds ratio (DOR), and AUC of circRNAs were associated with cancer diagnosis in each study. In this meta-analysis, we used a random-effects model when the heterogeneity test was  $I^2 > 50\%$ . On the contrary, the fixed-effect model was selected when  $I^2 < 50\%$ . In addition, meta-regression analysis was used to find the possible source of heterogeneity. Deeks' funnel plot asymmetry test was used for evaluating the potential publication bias. The value of  $p < 0.05$  was considered as statistical significance.

## Results

### Search and description of the studies

In this article, we assessed the circRNA expression in colorectal cancer as a potential biomarker for diagnosis of human CRC. The char-

acteristics of the studies included in this analysis were summarized in **Table 1**. A total of 489 patients and 407 normal samples from six studies published between January 2015 and December 2018 were collected in this meta-analysis [28, 33-37]. The searching process of the studies in this meta-analysis was shown in **Figure 1**.

### Quality assessment

**Figure 2** showed the quality assessment of the studies using the QUADAS-2 evaluation tool. The QUADAS-2 checklist contains four items (including patients selection, index test, reference standard, flow and timing), and the former three items assessed applicability concerns, while the entire four items evaluated the risk of bias. In **Figure 2**, the red circle represents the high risk, the yellow represent the unclear risk, the green circle represent the low risk. The quality assessment showed that all the publications had low risk in applicability concerns, indicating they are all high quality in applicability concerns.

### Meta-analysis

In the meta-analysis, the pooled sensitivity was 0.85 [95% confidence interval (CI): 0.78-0.89] and the specificity was 0.72 [95% CI: 0.65-0.78] (see **Figure 3**). Additionally, the PLR and NLR were 2.99 (95% CI: 2.43-3.68) and 0.21 (95% CI: 0.16-0.29), respectively (see **Figure 4**). The pooled diagnostic odds ratio (DOR) was 13.95 [95% CI: 9.75-19.97] and the value of the AUC was 0.84 [95% CI: 0.81-0.87] (see **Figures 5 and 6**). Significant heterogeneity across the studies was detected, shown in the **Table 2**. At the same time, we further carried out a series of analyses to investigate the source of heterogeneity.

### Threshold effect analysis

In this part, we performed Spearman's rank correlation to evaluate the threshold effect. The results showed that the Spearman correlation coefficient was -1.00 ( $P = 1.00$ ). In consequence, the value indicated no threshold effect.

### Subgroup analyses

We used the subgroup analysis on the basis of the year of publication and quantitative method. The detailed results were shown in **Table 2**.

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**Table 1.** Characteristics of the six studies included in the meta-analysis

Author	Year	Sample size		CircRNA	Method	Diagnostic power				Study design	Age (years)		Gender	
		Control	Case			Sensitivity	Specificity	AUC	Cutoff		< 60	≥ 60	Male	Female
Li_xiaomin [33]	2018	69	69	circITGA7	RT-qPCR	0.9275	0.6667	0.8791	NA	CRCT-ANT	36 <sup>a</sup>	33 <sup>b</sup>	36	33
Ji [34]	2018	64	64	hsa_circ_0001649	qRT-PCR	0.828	0.781	0.857	NA	CRCT-ANT	22	42	53	11
Wang [35]	2018	102	102	hsa_circ_0000567	qRT-PCR	0.8333	0.7647	0.8653	0.47	CRCT-ANT	55 <sup>a</sup>	47 <sup>b</sup>	58	44
Zhuo [36]	2017	40	122	hsa_circ_0003906	qRT-PCR	0.803	0.725	0.818	NA	CRCT-ANT	34	88	89	33
Wang [37]	2015	31	31	hsa_circ_001988	qRT-PCR	0.68	0.73	0.788	6.04	CRCT-ANT	15 <sup>a</sup>	16 <sup>b</sup>	19	12
Li_jinyun [28]	2018	101	101	hsa_circ_0000711	qRT-PCR	0.91	0.58	0.81	3.37	CRCT-ANT	43 <sup>a</sup>	58 <sup>b</sup>	59	42

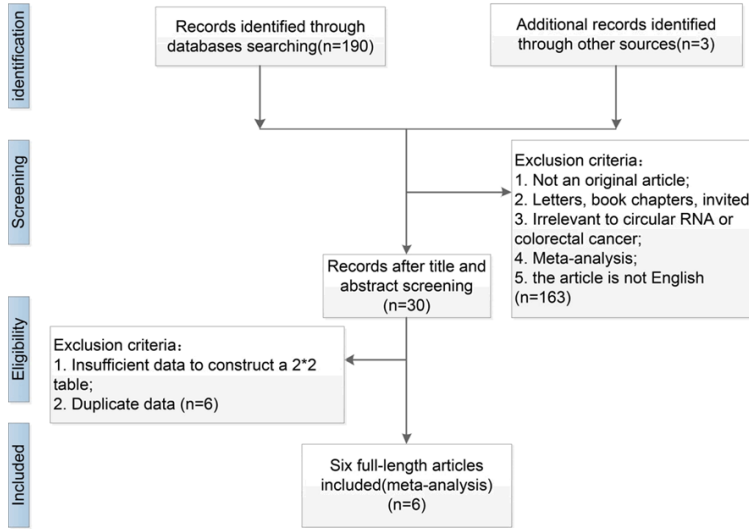
CircRNA = circular RNA, Control = adjacent or normal tissues, Case = colorectal cancer tissues, AUC = area under the curve, NA = not available, CRCT-ANT = colorectal cancer tissues and adjacent or normal tissues, the superscript 'a' represent ≤ 60, the superscript 'b' represent > 60.

**Table 2.** Characteristics of diagnostic accuracy and heterogeneity

Subgroups	Sensitivity (95% CI)	I <sup>2</sup> (%) sensitivity	Specificity (95% CI)	I <sup>2</sup> (%) specificity	PLR (95% CI)	I <sup>2</sup> (%) PLR	NLR (95% CI)	I <sup>2</sup> (%) NLR	DOR (95% CI)	I <sup>2</sup> (%) DOR	AUC
All_studies [28, 33-37]	0.85 (0.78-0.89)	67.57	0.72 (0.65-0.78)	55.55	2.99 (2.43-3.68)	0.00	0.21 (0.16-0.29)	52.9	13.95 (9.75-19.97)	70.55	0.84
Quantitative method											
qRT-PCR [28, 34-37]	0.83 (0.76-0.88)	61.79	0.73 (0.65-0.80)	63.46	3.04 (2.38-3.88)	0.00	0.24 (0.18-0.31)	43.01	12.91 (8.93-18.64)	62.74	0.85
Publication year											
after 2015 [28, 33-36]	0.86 (0.81-0.90)	55.09	0.71 (0.63-0.78)	63.3	2.96 (2.36-3.7)	0.00	0.19 (0.14-0.27)	17.02	15.18 (10.52-21.9)	55.84	0.86

95% CI = 95% confidence interval, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, DOR = Diagnostic Odds Ratio, AUC = area under the curve.

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**Figure 1.** The searching process of studies in this meta-analysis.

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ji 2018	?	+	+	+	+	+	+
Li_jinyun 2018	●	+	+	+	+	+	+
Li_xiaomin 2018	?	+	+	+	+	+	+
Wang 2015	●	+	+	+	+	+	+
Wang 2018	●	+	+	+	+	+	+
Zhuo 2017	?	+	+	+	+	+	+

● High      ? Unclear      + Low

**Figure 2.** Methodological quality summary.

The heterogeneity of the DOR was lower in the studies using qRT-PCR method than others ( $I^2$ , 62.74% vs. 70.55%). There was an analogous result in that there was less heterogeneity observed in studies with the year of publication ( $I^2$ , 55.84% vs. 70.55%).

### Meta-regression analysis

To further explore the source of heterogeneity, we performed the meta-regression analysis. For the aspect of sensitivity, there was no significant correlation between quantitative method ( $p = 0.90$ ) and publication year ( $p = 0.69$ ). For the aspect of specificity, there was a similar result with no significant correlation in method

( $p = 0.10$ ) and publish year ( $p = 0.25$ ) (see **Figure 7**).

### Publication bias

Deeks' funnel plot asymmetry test was used for publication bias (see **Figure 8**) and the value indicated no publication bias ( $p = 0.23$ ).

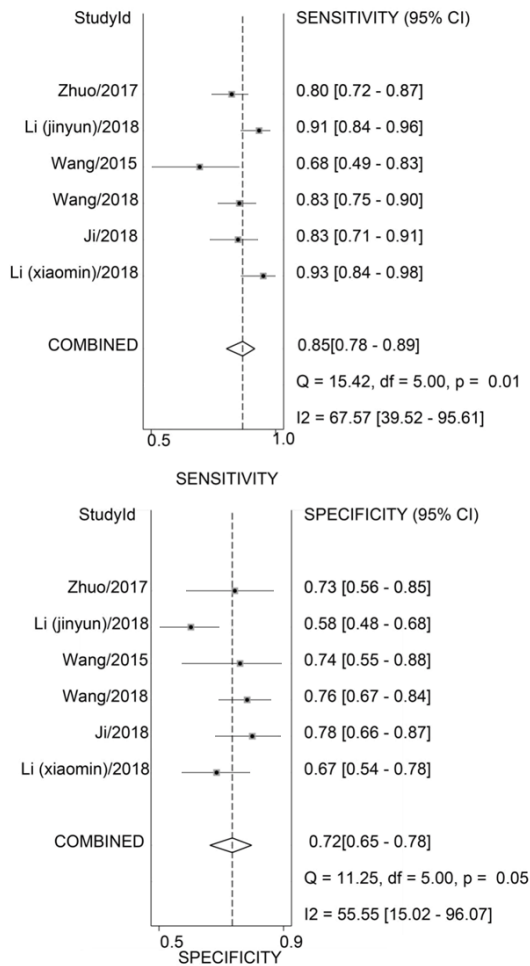
### Discussion

It has been reported that the circular RNA is more stable than the linear mRNA [38, 39]. Therefore, it could serve as a candidate biomarker for cancer diagnosis. There have been several reports about the associations between cir-

cRNAs and various tumors, and systematic studies were carried out by Yuan [29] and Wu [30] with supporting results for the diagnostic value of circRNAs in cancers. Recently, a significant amount of circRNAs were identified from colorectal cancer [5, 40]. However, there have been no systematic studies about the diagnostic accuracy of circRNAs in colorectal cancer except the study of Wang [31], reporting the diagnostic value of circRNAs in digestive system tumors. In this study, we selected six studies from public databases and other search engines to evaluate the diagnostic value of circRNAs for human colorectal cancer. All studies stated that the patient did not accept any adjunctive treatments before the surgery. As far as we know, this is the first meta-analysis discussing the diagnostic value of circRNAs for CRC.

Based on the selected studies, we assessed the diagnostic value of circRNAs as biomarkers for CRC. In this meta-analysis, sensitivity and specificity are the statistical indicators [30]. The value of DOR is an important indicator for test performance [41]. The value of AUC ranging from 0.75 to 1 is accep [42, 43]. As for the overall circRNAs expressions in colorectal cancer, the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and AUC values with the corresponding 95% CI were 0.85 (95% CI: 0.78-0.89), 0.72 (95% CI: 0.65-0.78), 2.99 (95% CI: 2.43-3.68), 0.21 (95% CI: 0.16-0.29), 13.95 (95% CI: 9.75-19.97) and 0.84 (95% CI: 0.81-0.87), respec-

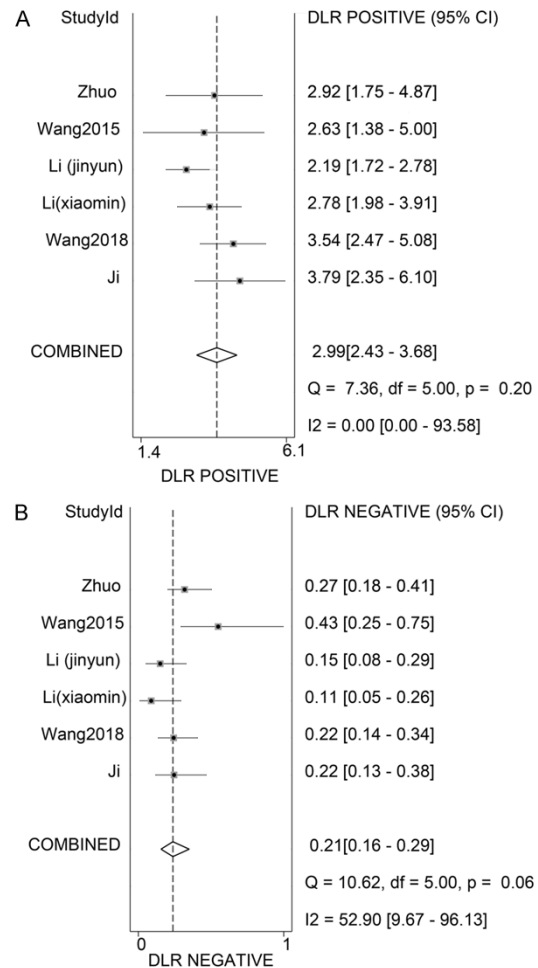
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**Figure 3.** Forest plot of sensitivity, specificity for diagnosis of circRNAs in CRC.

tively. These indicators suggested that circRNAs can be used as diagnostic biomarkers for CRC.

It was worth mentioning that there was heterogeneity in this study. In order to evaluate the threshold effect, we adopted the Spearman's correlation coefficient and the value of Spearman correlation coefficient is  $-1.00$  ( $P = 1.00$ ), indicating no existing threshold effect. Then we adopted a subgroup analysis to examine the heterogeneity in pre-specified subgroups. Heterogeneity was detected when stratified by quantitative method and the year of publication. The heterogeneity was decreased when we sub-grouped the samples by quantitative method ( $I^2, 62.7$  vs.  $70.5$ ) and publication year ( $I^2, 55.8$  vs.  $70.5$ ). The stratified analysis results suggested that the qRT-PCR quantitative method of study should be carried out to decrease the heterogeneity in the future. In

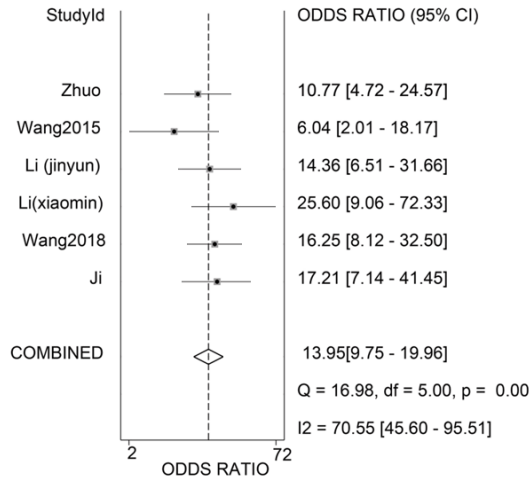


**Figure 4.** Forest plot of PLR (A), NLR (B) for diagnosis of circRNAs in colorectal cancer.

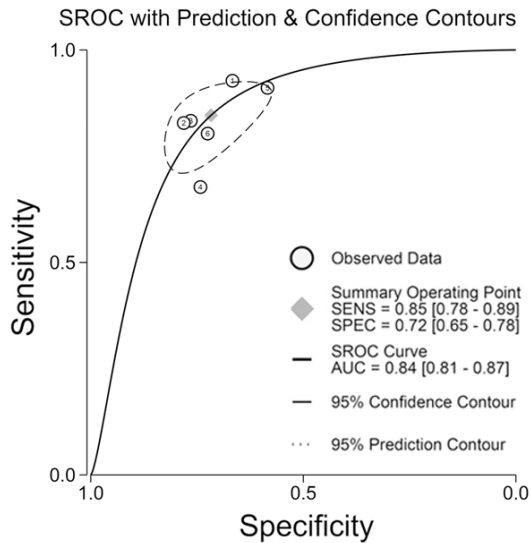
addition, we performed the univariate meta-regression based on the variables, including publication year and quantitative method. The results indicated no difference between quantitative method and publication year. On account of the missing data, we had no further investigation into other factors which contributed to the heterogeneity, including age, gender.

There were some shortcomings in the study. First, because the enrolled subjects were from Asia, it is possible to overlook the diagnostic performance of different ethnicities. Second, on account of missing data from the included studies, there was no analysis in some variables (such as, age, gender). Third, the sample sizes in the included studies were small and the diagnostic accuracy might not be equally distributed. Hence, in the future, large-scale stud-

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**Figure 5.** Diagnostic odds ratio of circular RNAs in colorectal cancer.



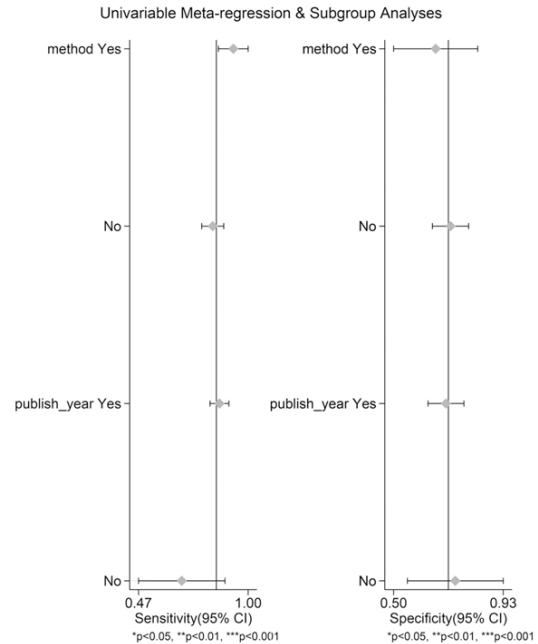
**Figure 6.** SROC of circular RNAs in diagnosis of colorectal cancer.

ies are required to confirm the diagnostic accuracy of circRNAs for colorectal cancer.

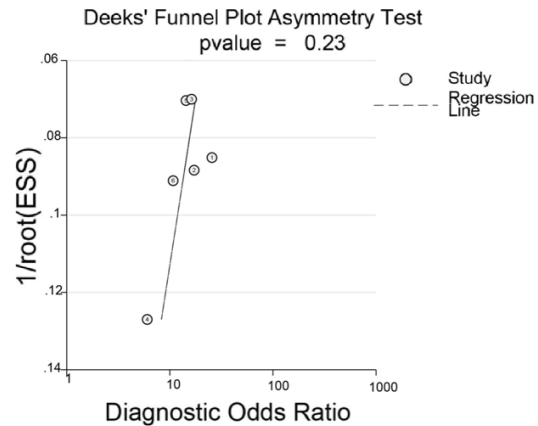
In conclusion, circRNA may be suitable as a diagnostic biomarker for colorectal cancer. More studies with large-scale samples should be carried to further confirm our result.

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**Figure 7.** Univariate meta-regression & Subgroup analyses.



**Figure 8.** Deeks' funnel plot evaluating the potential publication bias in meta-analysis.

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### Disclosure of conflict of interest

None.

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