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

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Abstract

Background: Circular RNA (circRNAs) is a new star in the network of noncoding RNA, regarded as a key control factor in numerous tumors. The purpose of our study was to evaluate the clinical, prognostic and diagnostic role of circRNAs in colorectal cancer. And all the articles were qualified by the Newcastle-Ottawa Scale.

Methods: An online search of electronic databases, including PubMed, the 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: Diagnostic value of pooled results showed that the area under the curve (AUC) was 0.82, from the control group to identify the sensitivity of the patients with colorectal cancer was 83%, specificity of 72%. In terms of prognostic role, carcinogenic circRNAs has a negative effect on overall survival (OS: HR = 2.29, 95% CI: 1.50-3.52), tumor suppressor circRNAs expression increase associated with longer survival (OS: HR = 0.37, 95% CI: 0.22-0.64). On the clinical characteristics, highly carcinogenic circular RNA expression and abnormal adverse clinical outcomes. The consequences of the tumor suppressor circular RNA, however, are completely opposite.

Conclusions: These results suggested that circRNAs may be a potential biomarker for the diagnosis and prognosis of colorectal cancer. **Keywords:** circular RNA, colorectal cancer, diagnosis, prognosis

Background

Circular RNA (circRNAs), consisting of a circular configuration through a typical 5' to 3'-phosphodiester bonds, is a novel class of endogenous non coding RNA [1–3]. CircRNAs plays a special role as molecular markers in many human diseases including tumors, due to their conservation, richness 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 interaction with RNA binding protein, regulating the stability of the mRNAs, regulate gene transcription, protein sponge microRNA and translation, etc. [5–7]. However, the underlying mechanisms and functions of circRNAs are still many uncertainties.

Extensive researches have proven that circRNAs played a major role in tumorigenesis, development of cardiovascular diseases, and pathogenesis of neurodegenerative diseases [8]. However, the differential expression of circRNAs and their definite functions is 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 late initial diagnosis stage and the high frequency of metastasis and recurrence [10]. In this study, we

proceeded to 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

Sources for the study include PubMed, Cochrane library, and the Web of Science online databases for circRNAs research, which was published in English before May 15, 2019. The search strategy in this study followed the following terms: (1) "circRNA" or "circular RNA" and (2) "colorectal cancer" or "colorectal carcinoma" or "colorectal tumor" or "CRC". Two researchers (Yuan and Guo) search the title, abstract and full text, to identify the appropriate article. Other researchers (Li), together with the former two researchers involved in the data extraction. Any disagreement is settled by a third researcher (Chen). Then extract the data from the selected article and populate it into the 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; (3) the studies detected the circRNA expression level, clinicopathological features, and prognosis of patients. Studies were excluded if the followed excluded criteria were met: (1) not about circRNAs or CRC; (2) data similar to previous studies; (3) case reports, animal experiments, reviews, and so on; (4) no applicable data.

Data extraction and quality assessment

Two investigators (Yuan and Guo) evaluated the eligibility of 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 circRNAs, following-up time and overall survival (OS); (c) the sensitivity and specificity of circRNAs for diagnosis; and (d) clinical data with age, gender, tumor 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 study. The quality assessment of each included study was carried out by two independent investigators (Yuan and Guo). And a third investigator (Li) discussed the differences. And the study was considered high quality if the score was ≥ 7 .

Statistical analysis

Statistical analysis was performed using STATA software (version 14). Merger odds ratio (OR) and 95% confidence interval (CI) was used to measure the clinical pathological parameters, sensitivity and

specificity, and hazard ratios (HRs) was used to assess the overall survival (OS). A chi-square test and I^2 statistic used to evaluate research between heterogeneity. When the I^2 value < 50%, the use of fixed effects model, think that there was no observable heterogeneity [12]. Otherwise, a random effects model was utilized. Sensitivity analysis was used to estimate potential sources of heterogeneity. Qualitative evaluation of publication bias was conducted through funnel plot, and quantitative evaluation was conducted by Begg and Egger inspection.

Results

Search Results

As showing in Fig. 1, 83 relevant literature was obtained from the database. Among them, 46 are full-text reviews and 27 are abstract reviews. In addition, 27 articles were ruled out for the following reasons: 5 were not circRNAs or CRC, 10 were without no relevant outcomes reported, 3 were review article, 1 was animal data, 8 had insufficient data. To sum up, there were 19 studies [13–31] in this study, with a total of 1307 patients, including 11 clinical parameters, 8 prognoses and 7 diagnoses.

Study characteristics

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

Clinicopathological parameters

The association between circRNAs and clinical features of CRC patients was 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 difference was found in terms of age, gender, tumor location.

Overall survival

As can be seen in Fig.2A, 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 the fixed-effect model was performed with no great heterogeneity ($I^2 = 0.0\%$, $p = 0.937$). In addition, low expression of tumor-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 the fixed-effect model was employed (Fig.2B).

Diagnosis analysis

Fig.3 provides the forest plot of the sensitivity and specificity of circRNAs. And the random-effect model was employed with high heterogeneity ($I^2 = 76.15\%$ and $I^2 = 48.29\%$). The pooled results was summarized as follows: sensitivity, 0.83, 95% CI: 0.75–0.88; specificity, 0.72, 95% CI: 0.66–0.78. Besides, the summary receiver operator characteristic (SROC) curve (Fig.4) were performed and the area under the ROC curve (AUC) was 0.82 (95% CI 0.78–0.85). Taken together, these results suggest that circRNAs had a good diagnostic accuracy for CRC.

Publication bias and sensitivity analysis

From the funnel plot, there is no publication bias in our study (Supplementary Figure 1). There was no obvious publication bias according to the 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 did not alter greatly when omitting studies one by one (Supplementary Figure 4). Furthermore, the Deek's funnel plot asymmetry test [31] reported no obvious publication bias ($p = 0.07$) for diagnosis analysis (Supplementary Figure 5).

Discussion

Recently, a considerable literature has grown up around the significant role of circRNAs, whereas there was no relevant meta-analysis on circRNAs expression in CRC. A total of 1307 cancer patients from nineteen eligible studies were collected and analyzed in this study, including seven on diagnosis, eight on prognosis, and eleven on clinicopathological features. For clinical features, high expression of oncogenic circRNAs was notable associated with poor clinical parameters while tumor-suppress circRNAs were opposite. For prognosis value, higher expression of oncogenic circRNAs indicated a poor survival while higher expression of tumor -suppressor circRNAs was contrary. In addition, the summarized result showed an area under the curve (AUC) of 0.82, with 83% sensitivity and 72% specificity for diagnosis value of circRNAs in CRC patients.

Our current study has observed a significant relationship between abnormal circRNAs expression and its diagnostic value in CRC patient. Since the tumor tissues, plasma, and even cell from patients with aberrant expressions of circRNAs can be easily detected, the measurement can be done conveniently and economically. Coupled with the structural stability of circRNAs, circRNAs was 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-analysis, only five meta-analysis [32–36] detected the association between the circRNAs and carcinoma. However, in the studies of wang et al, Chen et al and Li et al [32,33,34], only one study was included to investigate the relationship between the circRNAs and CRC. Li et al and Ding et al [35,36] assessed the diagnosis value of circRNAs for human cancers, in which five articles were included to investigate the diagnostic value of circRNAs for CRC, whereas they failed to discuss the role of circRNAs for CRC patients. In the present study, we collected all the relevant articles published to date and performed the meta-analysis including nineteen articles in 1307 CRC patients. Furthermore, we detected the prognosis and diagnosis value of circRNAs expression in CRC patients. Nonetheless, further large-scale studies are needed to confirm these results.

However, several limitations must be considered while 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. And then, a subgroup analysis was failed to finish according to different circRNAs for limited number of articles. Furthermore, the relatively small number of patients was included in this meta-analysis, so larger-scale studies would be necessary to verify the obtained results. At last, several studies did not provide HRs with their 95% CI in the article, so we need to extract them from the Kaplan-Meier survival curve.

Conclusion

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

Declarations

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.

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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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	circCRS7	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
Age	1.078	0.737-1.577	0.698	0.589	0.241-1.437	0.224
Gender(M/W)	1.114	0.757-1.639	0.968	0.805	0.491-1.320	0.390
Tumor size	1.769	1.097-2.852	0.019	0.658	0.382-1.132	0.131
Tumor location	0.888	0.572-1.380	0.598	0.902	0.480-1.694	0.748
Differentiation grade	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
Lymph node metastasis(Y/N)	3.357	2.160-5.215	0.000	0.389	0.116-1.307	0.127
Distant 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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