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Review

Diagnostic value of circular RNAs in colorectal cancer: A systematic review and meta-analysis

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ABSTRACT

Purpose: Mounting studies has revealed that circular RNAs (circRNAs) play a key role in tumorigenesis and might serve as promising biomarkers for cancer diagnosis. However, the diagnostic value of circRNAs in colorectal cancer (CRC) remains to be precisely elucidated.

Methods: All relevant literatures were searched using Cochrane Library, PubMed, Web of Science, EMBASE, CNKI, and WanFang databases up to June 2019. The quality of eligible studies was assessed in accordance with the Quality Assessment of Diagnostic Accuracy Studies-2 system. The summary receiver operator characteristic curve (SROC) and area under SROC (AUC) were applied for the quantitative assessment of diagnostic performance. Threshold effect, subgroup analysis, and meta-regression were adopted to explore the sources of heterogeneity. Deeks' funnel plot and sensitivity analysis were conducted to examine the publication bias and stability of meta-analysis, respectively.

Results: A total of 13 eligible studies involving 2190 subjects and 14 different kinds of circRNAs were enrolled. The pooled sensitivity, specificity, and AUC were 0.78 [95% confidential interval (CI): 0.70-0.84], 0.71 (95% CI: 0.65-0.76), and 0.80 (95% CI: 0.76-0.83), respectively. Subgroup analysis showed that studies involving ≥ 100 cases had higher sensitivity but lower specificity than those involving < 100 cases. Meta-regression revealed that sample size might be the potential source of heterogeneity. Sensitivity analysis and Deeks' funnel plot indicated that our results were relatively robust and had no publication bias.

Conclusion: CircRNAs possess relatively moderate diagnostic accuracy and might serve as potential diagnostic biomarkers for colorectal cancer. Future large-scale studies are needed to confirm the diagnostic value of circRNAs.

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies around the world, with an estimation of 1.3 million new cases and over 0.7 million deaths annually [1]. In China, CRC has the fifth highest mortality rate among all cancer [2]. The survival rate of CRC is inversely associated with the cancer stage at diagnose, with up to 90% five-year survival rate for stage I and less than 8% for stage IV [3]. Thus, early diagnosis of CRC is critical for improvement of survival outcome.

Currently, colonoscopy remains the gold standard for CRC screening because of its high diagnostic accuracy. However, its invasive and intolerant nature has limited the wide application. Less-invasive diagnostic methods, such as fecal occult blood testing and carcinoembryonic antigen (CEA) still have not been used broadly due to low sensitivity or specificity for CRC detection [4,5]. Therefore, there is an urgent need to discover more accurate and acceptable method for CRC screening. The emerging use of some molecular markers as potential biomarkers has been shown in CRC diagnosis [6–8]. Circular RNAs (circRNAs), which have been extensively reported to play a key role in tumorigenesis, are thought to be promising biomarkers for early detection of cancer [9,10].

CircRNAs, emerging as a novel type of endogenous noncoding RNAs, are generated from back-splicing of precursor RNAs and characterized by a covalently closed continuous loop [11,12]. Due to the unique loop structure, circRNAs are resistant to degradation by exonucleases, and thus more stable and evolutionarily conserved than microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) [13]. Numerous of articles have confirmed that circRNAs can regulate the initiation and progression of different types of cancers through diverse

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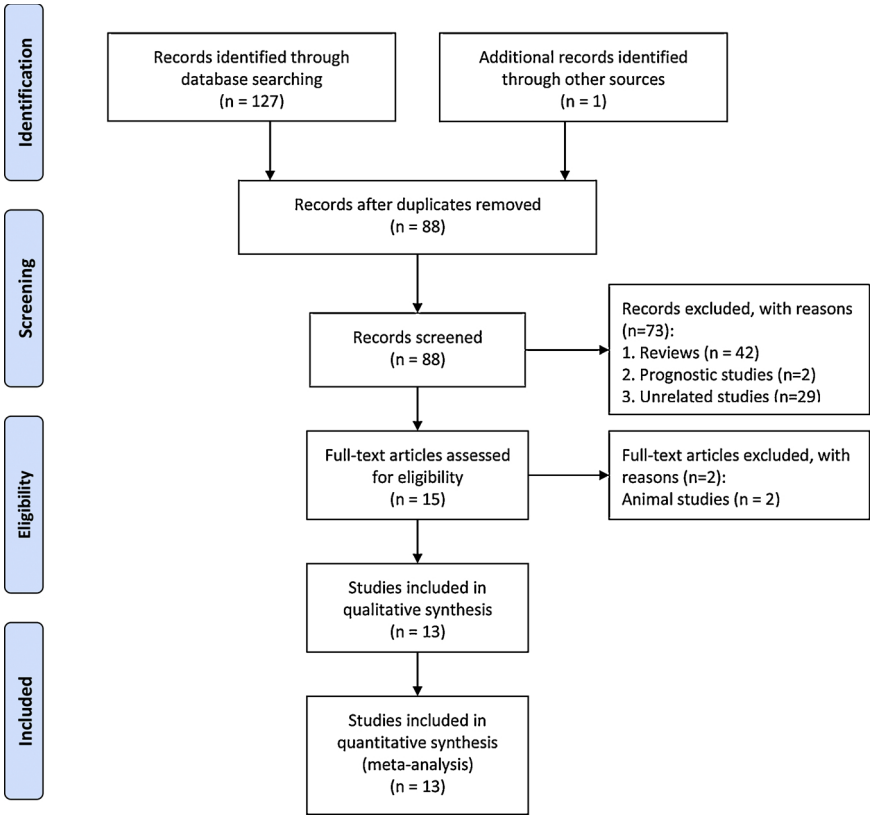

Fig. 1. The flow chart of literature selection process.

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

Author	Year	Country/ Ethnicity	Expression level	CircRNAs profiles	Specimen source	Sample size (case/control)	TP	FP	FN	TN	Sensitivity	Specificity	AUC
Xuning Wang	2015	China/ Asian	down-regulated	hsa_circ_001988	tissues	31/31	21	8	10	23	0.680	0.730	0.788
Fan Zhuo	2017	China/ Asian	down-regulated	hsa_circ_0003906	tissues	122/40	98	11	24	29	0.803	0.725	0.818
Kuei-Yang Hsiao	2017	China/ Asian	up-regulated	has_circ_0001313	tissues	131/76	122	20	9	56	0.931	0.738	0.884
Peili Zhang	2017	China/ Asian	down-regulated	hsa_circ_103809	tissues	170/170	113	52	57	118	0.664	0.695	0.699
		China/ Asian	down-regulated	hsa_circ_104700	tissues	170/170	116	80	54	90	0.682	0.529	0.616
Cristina Barbagallo	2018	Italy/ Caucasian	up-regulated	hsa_circ_0000284	serum	20/20	14	4	6	16	0.710	0.800	0.771
Feng Wang	2018	China/ Asian	down-regulated	hsa_circ_0014717	tissues	46/46	20	6	26	40	0.432	0.870	0.683
Jianjun Wang	2018	China/ Asian	down-regulated	hsa_circ_0000567	tissues	102/102	85	24	17	78	0.833	0.765	0.865
Jinyun Li	2018	China/ Asian	down-regulated	hsa_circ_0000711	tissues	101/101	92	42	9	59	0.910	0.580	0.810
Wanchuan Zhang	2018	China/ Asian	up-regulated	hsa_circ_0007534	plasma	112/46	103	22	9	24	0.920	0.522	0.780
Wenxin Ji	2018	China/ Asian	down-regulated	hsa_circ_0001649	tissues	64/64	53	14	11	50	0.828	0.781	0.857
Haoyu Ruan	2019	China/ Asian	down-regulated	hsa_circ_0002138	tissues	35/35	22	9	13	26	0.629	0.743	0.725
Jianxin Ge	2019	China/ Asian	down-regulated	hsa_circ_0142527	tissues	41/41	34	8	7	33	0.829	0.805	0.818
Xiangnan Li	2019	China/ Asian	up-regulated	hsa_circ_0006990	plasma	60/43	42	15	18	28	0.700	0.651	0.724

biological functions, including regulation of gene transcription, serving as miRNA sponges, interaction with proteins, and translation into peptides [14]. Recently, a series of studies have revealed that dysregulated circRNAs in colorectal cancer might correlate with pathological features and clinical outcomes, indicating the potential biomarker's role in the diagnosis of CRC [15].

However, because of the variances in study design, sample size, and specimen source among different studies, the clinical diagnostic value of circRNAs in colorectal cancer has not been precisely elucidated. Therefore, we performed this meta-analysis of data from all relevant literatures to explore the relationship between dysregulated circRNAs and CRC diagnosis.

2. Methods

2.1. Literature search strategy

The present meta-analysis was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. Cochrane Library, PubMed, Web of Science, EMBASE, CNKI, and WanFang online databases were searched up to June 2019 for pertinent literatures adopting the following search strategy: (circRNAs OR Circular RNAs) AND (colorectal neoplasm OR colorectal tumor OR colorectal carcinoma OR colorectal cancer OR colon cancer OR rectal cancer) AND (diagnosis OR sensitivity OR

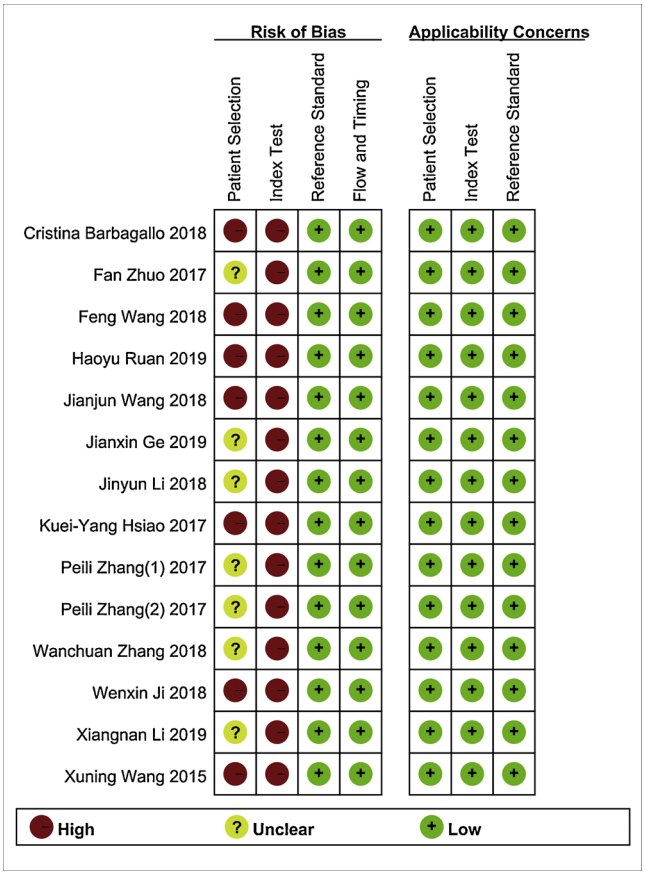

Fig. 2. Methodological quality summary.

specificity OR ROC curve OR receiver operating characteristic curve). The references of relevant articles were also manually retrieved to ensure all eligible studies were included. Two authors (Zhao and Liu) carefully screened the retrieved literatures through titles, abstracts and full-text reading. Any disagreement was resolved through discussion with the third author (Zou).

2.2. Literature selection criteria

Eligible studies adhered to the following criteria: (a) studies investigated the diagnostic value of circRNAs in human colorectal cancer; (b) colorectal cancer was histologically confirmed by pathologists; (c) expression of circRNAs was determined using quantitative reverse transcription polymerase chain reaction (RT-PCR); (d) studies provided available data to reconstruct the diagnostic 2 × 2 contingency table or data could be available through contacting with the corresponding author by email. Exclusion criteria were set as follows: (a) duplicated studies; (b) reviews, meta-analyses, basic studies, prognostic studies, and letters; (c) studies lacking sufficient data to construct 2 × 2 contingency table.

2.3. Data extraction and quality assessment

The following information was extracted from each included literature: first author's name, publication year, circRNAs profiles, expression level, specimen source, sample size, and diagnostic indexes (true positive, false positive, false negative, true negative values, sensitivity, specificity, and AUC). The quality of enrolled studies was assessed by two authors (Zhao and Liu) in accordance with the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) based on four dimensions ("Patient Selection", "Index Test", "Reference Standard", and "Flow and Timing") in two categories ("Risk of Bias" and "Applicability Concerns") [17]. Any disagreement was resolved by consensus after discussion.

2.4. Statistical analyses

Statistical analyses were performed using Review Manager 5.2, Meta-DiSc 1.4, and STATA 14.0 software. Review Manager 5.2 software was employed to assess the quality of enrolled studies. Meta-DiSc 1.4 software was adopted to examine the threshold effect through spearman correlation analysis. The bivariate mixed-effects model was applied to calculate the pooled sensitivity, specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), and diagnostic odds ratio (DOR) with their 95% confidence intervals (CIs). The summary receiver operator characteristic (SROC) curve and area under the curve (AUC) were calculated for the quantitative assessment of diagnostic value. Heterogeneity caused by non-threshold effects across studies was evaluated using Cochran's Q tests and I-squared (I^2) statistics, where either $P < 0.1$ or $I^2 > 50\%$ indicated the existence of significant heterogeneity. A bivariate boxplot was applied to evaluate the heterogeneity of each article. Meta-regression and subgroup analysis were conducted to explore the sources of heterogeneity. Furthermore, Fagan's nomogram was employed to examine the post-test probability. Sensitivity analysis was conducted to analyze the stability of meta-analysis. Deeks' funnel plot was used to examine publication bias. P value less than 0.05 was considered as significant differences.

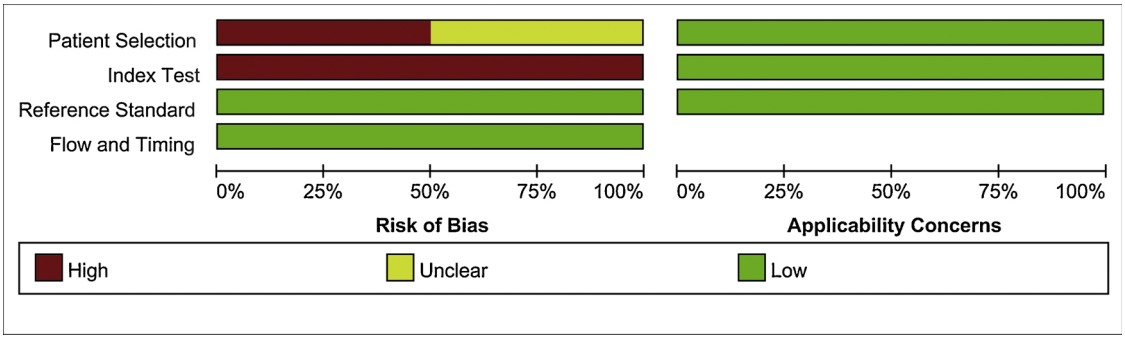

Fig. 3. Methodological quality graph.

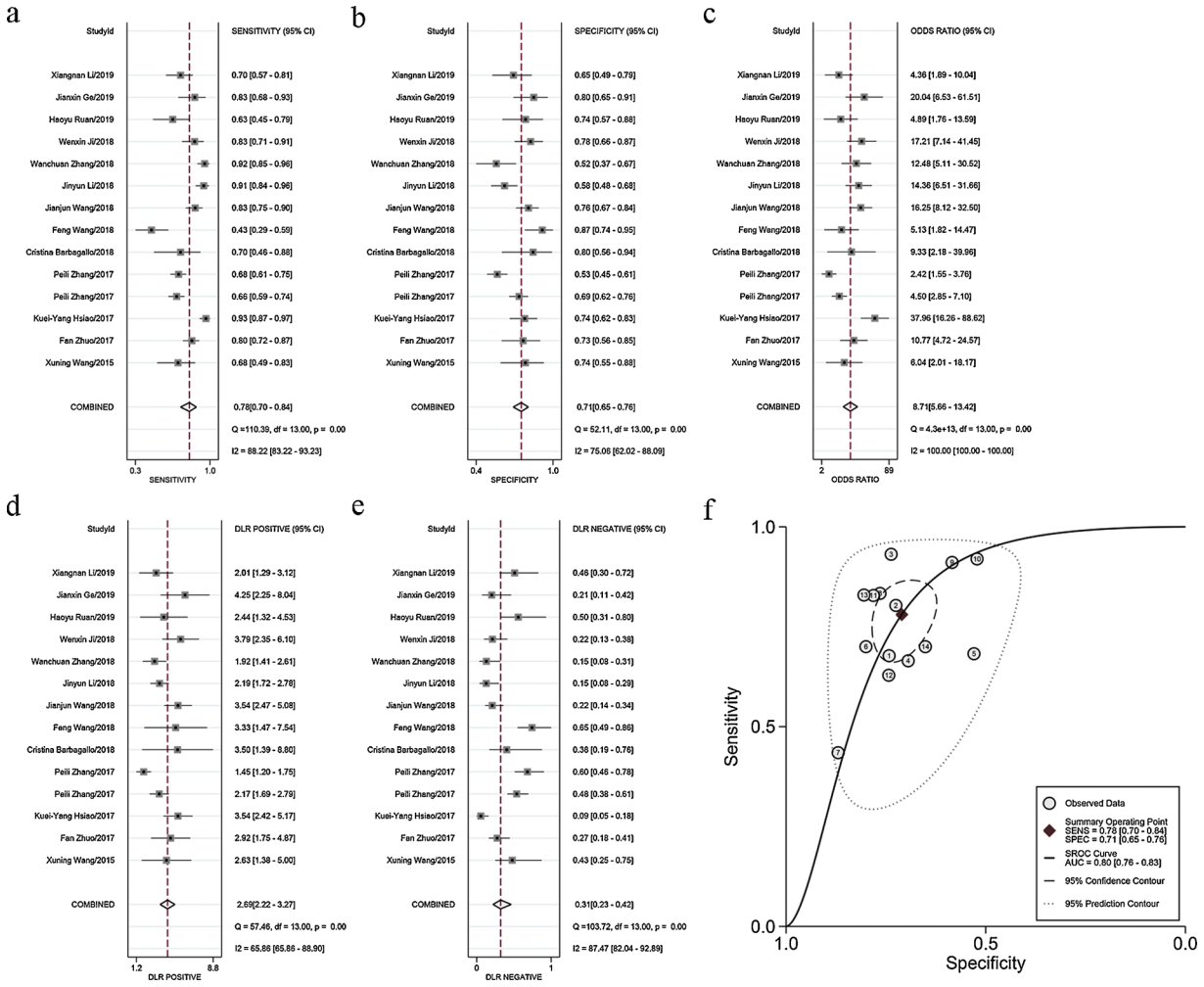

Fig. 4. Pooled diagnostic accuracy of circRNAs in colorectal cancer. (a–e) forest plots of sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, and negative likelihood ratio. (f) summary receiver operator characteristic curve.

3. Results

3.1. Literature search and study characteristics

A total of 128 potentially relevant articles were retrieved from database searching and other sources. After excluding 40 duplicate articles, titles and abstracts of the remaining 88 articles were screened and then 73 articles were removed because they were reviews (n = 42), prognostic studies (n = 2), and other unrelated studies (n = 29). The remaining 15 articles were further assessed by full-text reading. 2 articles were excluded due to animal studies. Eventually, 13 eligible studies involving 2190 subjects were enrolled in this meta-analysis [18–30]. The flow chart of literature selection process was shown in Fig. 1.

The characteristics of the included publications are listed in Table 1. A total of 14 different kinds of circRNAs were used to evaluate the diagnostic value for colorectal cancer. The specimen source of circRNAs was tissues (n = 11), plasma (n = 2), and serum (n = 1), respectively. All cancer cases were verified by histopathological method and the controls included paired adjacent non-cancer tissue, normal tissue, or blood from healthy subjects. The expression levels of circRNAs were determined by RT-PCR. Most of the circRNAs were down-regulated in colorectal cancer. Furthermore, the sample size of each study ranged from 40 to 340, with 143 as the median value.

3.2. Quality assessment

The quality assessment of all enrolled studies was shown in Fig. 2 and 3. In terms of Flow and Timing, Reference Standard, and Applicability Concerns, all enrolled studies were at low risk of bias. However, the enrolled studies were case-control studies and the diagnostic value of circRNAs for colorectal cancer was measured in AUC. Half studies showed high risk of bias in Patient Selection and all studies had high risk of bias in Index Test because of the deficiencies in study design, including studies enrolling participants with confirmed diagnoses and index test conducting after the reference standard. Therefore, the quality of the included studies was relatively moderate.

3.3. Pooled diagnostic accuracy

A significant heterogeneity was detected in the pooled sensitivity (I^2 = 88.22%, P < 0.001) and specificity (I^2 = 75.06%, P < 0.001).

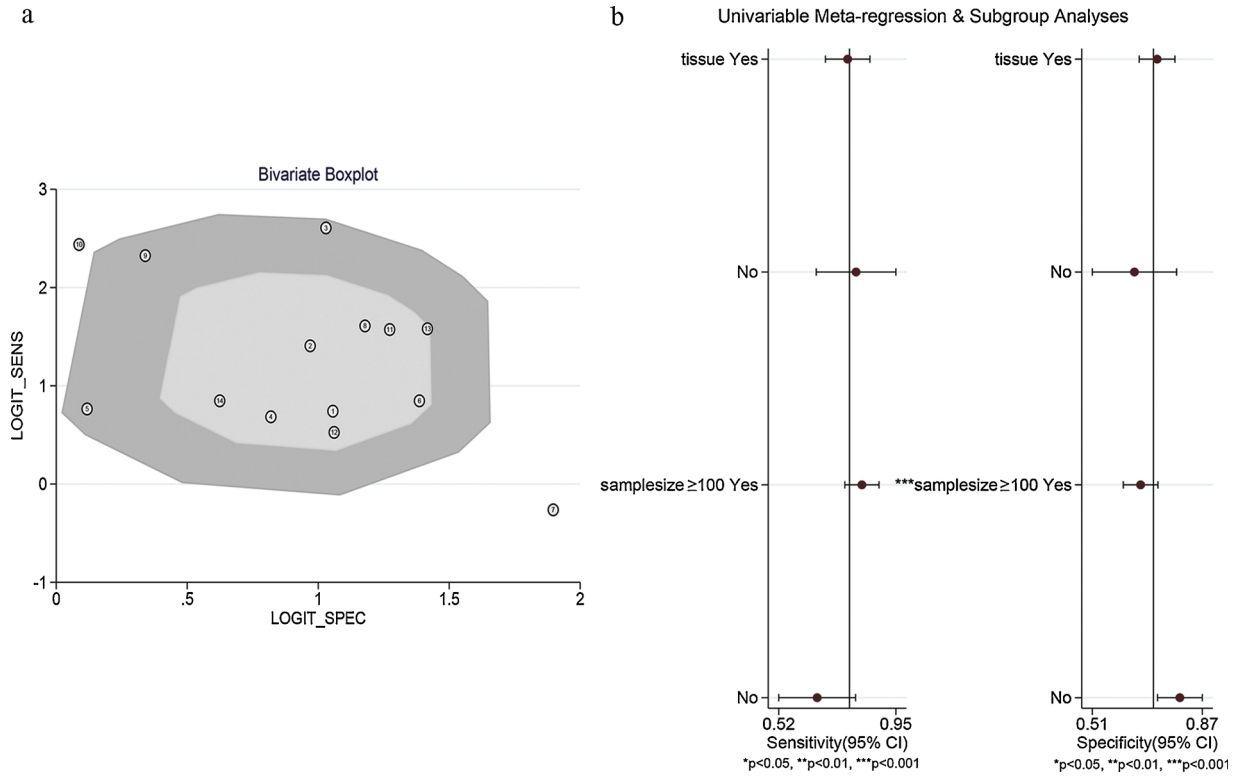

Fig. 5. The source of heterogeneity. (a) bivariate boxplot. (b) univariable meta-regression analysis.

Therefore, a random-effects model was applied to evaluate the pooled diagnostic accuracy. The pooled sensitivity, specificity, PLR, NLR, and DOR were 0.78 (95% CI: 0.70-0.84), 0.71 (95% CI: 0.65-0.76), 2.69 (95% CI: 2.22–3.27), 0.31 (95% CI: 0.23-0.42), and 8.71 (95% CI: 5.66–13.42), respectively. The area of summary receiver operator characteristic (SROC) curve was 0.80 (95% CI: 0.76-0.83), indicating that circRNAs possessed a relatively moderate diagnostic accuracy for human colorectal cancer (Fig. 4).

3.4. Source of heterogeneity

First, Spearman correlation analysis was conducted to examine whether heterogeneity was caused by threshold effect. Spearman correlation coefficient was 0.266 with a P value of 0.358, indicating that threshold effect was not the source of heterogeneity.

Secondly, a bivariate boxplot was performed to evaluate the heterogeneity of each study. As shown in Fig. 5a, 2 studies (study 7 and study 10) were not located in the boxplot. In Study 7, the circRNA was extracted from tissue and the sample size was less than 100, while the circRNA in study 10 was derived from plasma and the sample size was more than 100, implying that specimen source and sample size might be the potential cause of heterogeneity.

The subsequent subgroup analysis based on specimen source and sample size was performed. As presented in Table 2, studies using tissue specimen exhibited higher specificity, DOR, AUC but lower sensitivity than those in blood specimen subgroup. Additionally, studies involving $\geq$ 100 cases showed higher sensitivity, DOR but lower specificity than those in the subgroup involving $<$ 100 cases, while the AUC was similar between the two subgroups. Meta-regression analysis (Fig. 5b) indicated that sample size acted as the potential source of heterogeneity ($P = 0.01$), while no statistically significance between specimen source and pooled sensitivity and specificity ($P = 0.61$).

3.5. Sensitivity analysis and publication bias

As indicated in Fig. 6, influence analysis showed 2 outlier studies, while no outlier study was identified in outlier detection. After removing the two studies [23,28], the I^2 value for heterogeneity of sensitivity and specificity decreased from 88.22 to 84.14%, and from 75.06 to 51.95%, respectively (Table 2). Nevertheless, the pooled diagnostic accuracy indexes were comparable with those of the overall studies (sensitivity: 0.78 vs. 0.81; specificity: 0.71 vs. 0.71; AUC: 0.80 vs. 0.80), indicating that our results were relatively robust and not significantly influenced by any individual study.

Deeks' funnel plot asymmetry test was adopted to detect the publication bias. As displayed in Fig. 7, a P value of 0.38 indicated no publication bias in current meta-analysis.

3.6. Clinical diagnostic value of circRNAs in colorectal cancer

Fagan's nomogram was considered as a useful tool for evaluating the diagnostic value of circRNAs in clinical application. As shown in Fig. 8a, when pre-test probability was set at 20%, a 40% post-test probability with a PLR of 3 and a 7% post-test probability with an NLR of 0.31 were achieved. When 30% value was selected as the pre-test probability, the positive post-test probability would increase to 54%, while the negative post-test probability would decrease to 12%, as indicated in Fig. 8b.

4. Discussion

Mounting evidence has indicated the important role of circRNAs in the proliferation, invasion, and migration of multiple types of tumors, including lung cancer [31], ovarian cancer [32], hepatocellular carcinoma [33], colorectal cancer [34] and so on. Additionally, aberrant

Table 2
Assessment of diagnostic accuracy and heterogeneity in subgroup analysis.

Subgroups	Studies	Sensitivity (95% CI)	I^2 (%)	Specificity (95% CI)	I^2 (%)	PLR (95% CI)	I^2 (%)	NLR (95% CI)	I^2 (%)	DOR (95% CI)	I^2 (%)	AUC (95% CI)
Specimen source												
tissue	11	0.77 (0.68-0.85)	89.08	0.72 (0.66-0.78)	78.30	2.80 (2.23-3.50)	71.82	0.31 (0.22-0.45)	89.30	8.97 (5.36-14.99)	100	0.80 (0.76-0.83)
blood	3	0.80 (0.68-0.88)	84.09	0.64 (0.54-0.73)	48.24	2.24 (1.82-2.75)	0	0.31 (0.20-0.48)	70.77	7.18 (4.38-11.78)	77.28	0.75 (0.71-0.79)
Sample size												
≥ 100	9	0.83 (0.75-0.88)	89.39	0.67 (0.60-0.73)	77.72	2.50 (2.02-3.08)	74.94	0.26 (0.17-0.39)	89.93	9.64 (5.54-16.79)	100	0.79 (0.75-0.82)
< 100	5	0.66 (0.53-0.77)	73.99	0.80 (0.73-0.85)	0	3.25 (2.36-4.48)	0	0.43 (0.30-0.61)	66.85	7.61 (4.20-13.77)	86.25	0.81 (0.78-0.85)
Overall	14	0.78 (0.70-0.84)	88.22	0.71 (0.65-0.76)	75.06	2.69 (2.22-3.27)	65.86	0.31 (0.23-0.42)	87.47	8.71 (5.66-13.42)	100	0.80 (0.76-0.83)
Outliers excluded	12	0.81 (0.74-0.86)	84.14	0.71 (0.66-0.76)	51.95	2.80 (2.39-3.28)	19.14	0.27 (0.20-0.36)	81.18	10.47 (7.05-15.55)	100	0.80 (0.76-0.83)

expression of circRNAs in CRC have been confirmed to be associated with pathological features and clinical outcomes. For instance, Weng et al. found that circular RNA ciRS-7-A was notably up-regulated in CRC tissues and its overexpression was associated with advanced tumor stage, distant metastasis, and poor survival [35]. Zhu et al. revealed that the high expression of hsa_circ_0007142 in CRC tissues was correlated with the differentiation and lymphatic metastasis [36]. Wang et al. showed that the up-regulated circular RNA circPVT1 was closely associated with bad pathological features and poor prognosis in CRC patients [34]. Given their stable loop structure and intricate regulatory mechanisms, circRNAs might be promising biomarkers in the diagnosis of CRC. However, because of the variances in study design, sample size, and specimen source, the diagnostic results from different studies were inconsistent, leading us to comprehensively evaluate the feasibility of using circRNAs as CRC biomarkers.

The present study is the first meta-analysis to evaluate the diagnostic value of circRNAs in colorectal cancer. Our results indicated that the pooled sensitivity, specificity, DOR, and AUC were 0.78 (95% CI: 0.70-0.84), 0.71 (95% CI: 0.65-0.76), 8.71 (95% CI: 5.66–13.42), and 0.80 (95% CI: 0.76-0.83), respectively. The value of DOR is positively correlated with the discriminatory performance of diagnostic test [37]. AUC is commonly recognized as the most important index to evaluate the overall diagnostic performance of biomarkers and the value more than 0.75 is thought to be reasonable and acceptable [38]. According to our results, the value of DOR and AUC were 8.71 and 0.80, respectively, suggesting that circRNAs might serve as potential diagnostic biomarkers for colorectal cancer. CEA is the most extensively studied serum biomarker for colorectal cancer screening. Previous study indicated that the pooled sensitivity and specificity of CEA were 0.46 and 0.89, respectively [39]. Our study revealed that blood-derived circRNAs possessed higher sensitivity (0.80) but lower specificity (0.64). Furthermore, as reported, the AUC of CEA in CRC detection was 0.79 [40], which was higher than that of blood-derived circRNAs (0.75). It seemed that circRNAs did not show the superiority over CEA in terms of diagnostic accuracy. However, due to the limited number of enrolled studies, our results should be interpreted cautiously and needed to be confirmed by large-scale studies.

Significant heterogeneity was found in the pooled diagnostic indexes. A Spearman correlation coefficient of 0.266 ($P = 0.358$) indicated that threshold effect was not the main source of heterogeneity. A bivariate boxplot implied that specimen source and sample size might be the potential cause of heterogeneity. Therefore, we subsequently performed subgroup analysis based on specimen source and sample size. Our results revealed that studies using tissue specimen exhibited higher specificity but lower sensitivity than those in blood specimen subgroup. Additionally, studies involving ≥ 100 cases showed higher sensitivity but lower specificity than those in the subgroup involving < 100 cases. Meta-regression analysis indicated that sample size might acted as the potential source of heterogeneity. Sensitivity analysis and Deeks' funnel plot revealed that the present meta-analysis was relatively robust and showed no publication bias.

In spite of our best efforts to perform this comprehensive meta-analysis, there are still several inevitable limitations. First of all, the number of enrolled studies was relatively small, resulting in only three studies in the blood specimen subgroup, which might account for no statistically significance between specimen source and pooled diagnostic accuracy. More studies are warranted to validate the diagnostic value of circRNAs. Second, an ideal diagnostic biomarker should distinguish CRC patients from not only healthy people but also patients with benign disease, such as inflammatory bowel disease. However, the tissue or blood specimen in control group were derived from adjacent non-cancer tissue or healthy subjects, might resulting in an overestimation of diagnostic performance. Third, most of the enrolled studies were conducted in Asia. Further multi-center studies in different populations might be needed to confirm whether these results could apply equally to other ethnicities. Forth, all included studies adopted a

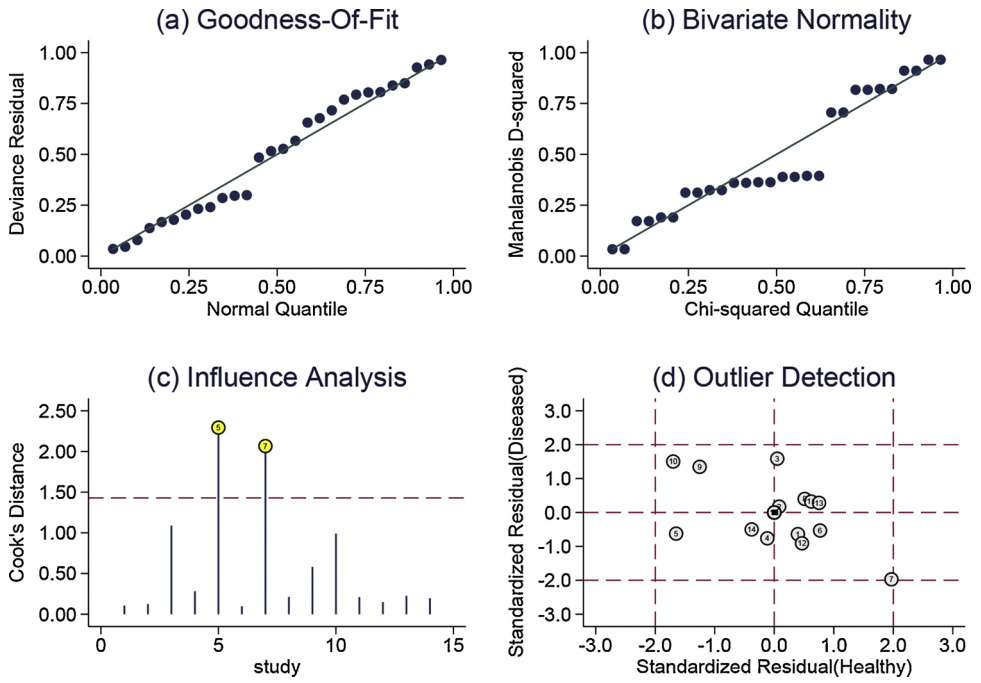

Fig. 6. Sensitivity analysis. (a) goodness of fit. (b) bivariate normality. (c) influence analysis. (d) outlier detection.

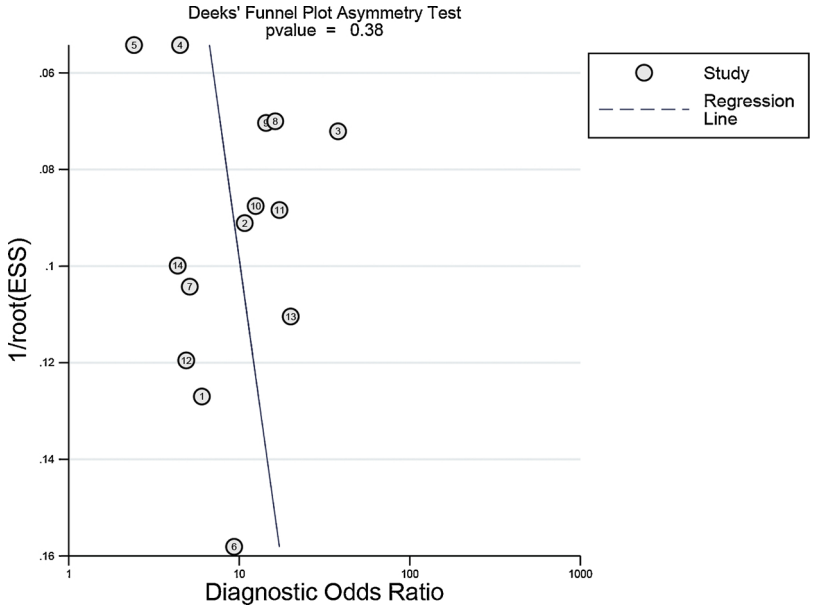

Fig. 7. Deeks' funnel plot evaluating the potential publication bias.

single circRNA to detect CRC. A panel of combined circRNAs might lead to a higher diagnostic accuracy. Thus, it might be necessary to assess the diagnostic practicality of combined circRNAs for CRC in the future research. Despite these limitations, our study is the first meat-analysis to evaluate the diagnostic value of circRNAs for CRC.

5. Conclusions

In conclusion, the present meta-analysis indicated that the pooled sensitivity, specificity, and AUC of circRNAs in CRC diagnosis were 0.78, 0.71, and 0.80, respectively. CircRNAs possess relatively moderate diagnostic accuracy and might serve as potential biomarkers for CRC. Future large-scale studies are needed to confirm the diagnostic value of circRNAs.

Declaration of Competing Interest

The authors declare no conflicts of interest in this work.

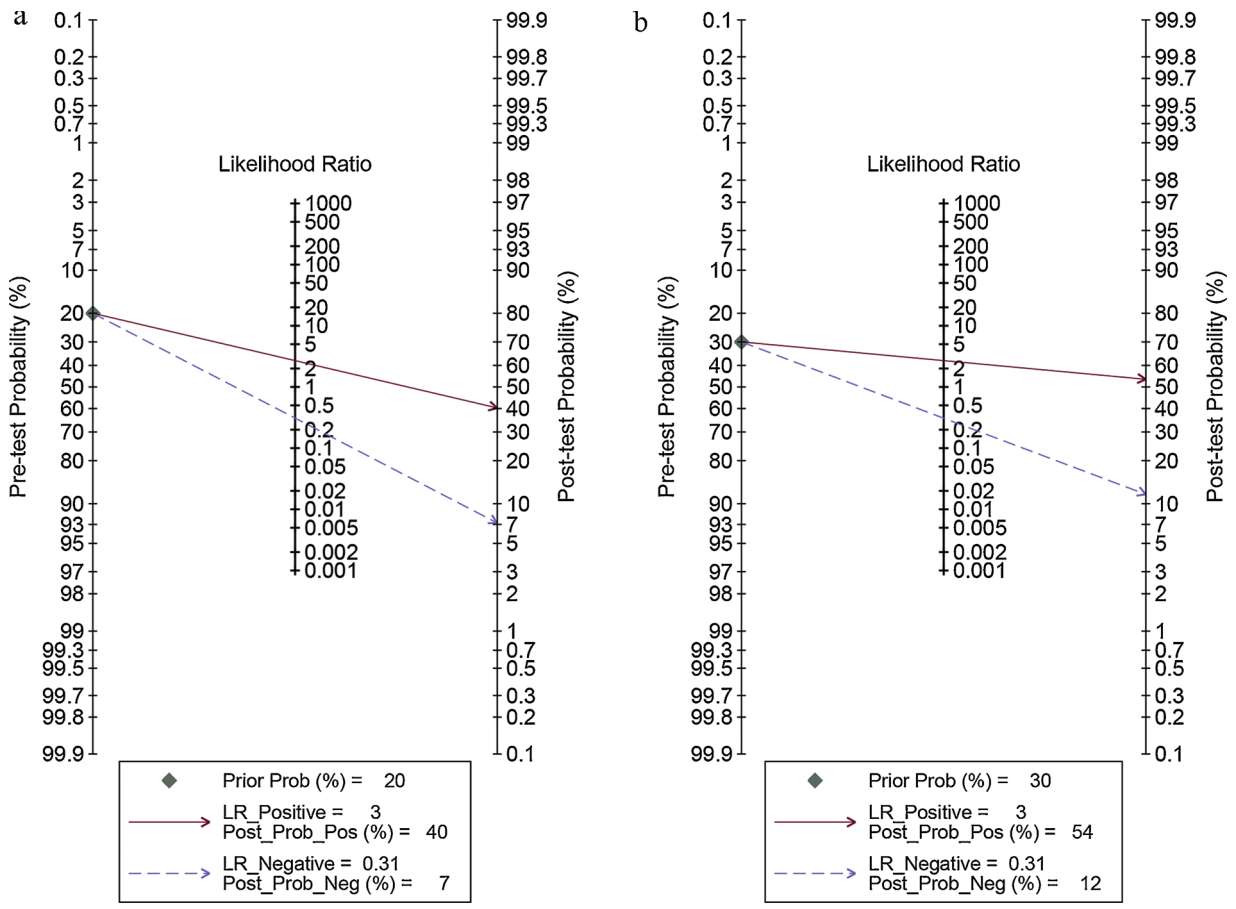

Fig. 8. Fagan's nomogram assessing the clinical diagnostic value of circRNAs in colorectal cancer. (a) the pre-test probability was set at 20%. (b) the pre-test probability was set at 30%.

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