ORIGINAL RESEARCH

Diagnostic value of circular RNAs as effective biomarkers for cancer: a systematic review and meta-analysis

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Hong Tan^{1,*} Li Gan^{2,*} Xiaoming Fan³ Limin Liu⁴ Shan Liu³

¹Department of General Surgery, Chengdu Integrated TCM & Western Medicine Hospital (Chengdu First People's Hospital), Chengdu, 610041, China; ²School of Medicine, University of Electronic Science and Technology of China, Key Laboratory for Human Disease Gene Study, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, 610054, China; ³Department of Laboratory Medicine, Affiliated Hospital of University of Electronic Science and Technology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, 610072, China; ⁴Jiangsu Institute of Hematology, the First Affiliated Hospital of Soochou University, Institute of Blood and Marrow Transplantation, Suzhou, 215006, China

*These authors contributed equally to this work

Correspondence: Limin Liu Jiangsu Institute of Hematology, the First Affiliated Hospital of Soochou University, Institute of Blood and Marrow Transplantation, No. 188 Shizi Street, Suzhou 215006, People's Republic of China Phone +86 152 6248 2466 Email Imliu@suda.edu.cn

Shan Liu

Department of Laboratory Medicine, Affiliated Hospital of University of Electronic Science and Technology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, No.32 West Second Section First Ring Road, Chengdu 610072, People's Republic of China Phone +861 345 868 6783 Email shanliusyy@163.com



Background: Increasing evidence has identified circular RNAs (circRNAs) as ideal molecular biomarkers for cancer diagnosis, therapy, and prognosis. However, the overall diagnostic efficiency of circRNAs remains unclear. Thus, this meta-analysis aimed to comprehensively evaluate the diagnostic accuracy of circRNA expression profiles for cancer. **Methods:** A literature search of online databases was conducted to identify all eligible studies. The quality of the studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. All statistical analyses were executed using STATA 14.0, Meta-DiSc 1.4, and Review Manager 5.2 software.

Results: A total of 32 studies, involving 2,400 cases and 2,295 controls, were included in the diagnostic meta-analysis. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and area under the curve were 0.79 (95% CI: 0.73-0.84), 0.73 (95% CI: 0.67-0.79), 2.9 (95% CI: 2.5-3.5), 0.29 (95% CI: 0.24-0.36), 10 (95% CI: 8-13), and 0.83 (95% CI: 0.79-0.86), respectively. The overall analysis suggested that circRNAs are useful diagnostic biomarkers for cancer. Subgroup analysis indicated that plasma samples had a better diagnostic performance than cancer tissue samples for cancer detection. Studies involving ≥ 100 cases or gastric cancer showed higher sensitivities than those including <100 cases or other cancers.

Conclusion: This meta-analysis revealed that circRNAs were significantly correlated with cancer diagnosis. In addition, circRNAs had good diagnostic accuracy and might serve as effective diagnostic biomarkers for cancer.

Keywords: circular RNAs, cancer, diagnosis, biomarkers, meta-analysis

Introduction

Circular RNAs (circRNAs), a novel class of endogenous noncoding RNAs (ncRNAs), are generated from back-splicing events and are characterized by a covalently closed continuous loop without 5' caps and 3' poly (A) tails.^{1,2} Owing to the closed continuous loop structure, circRNAs can escape exonuclease-mediated degradation; therefore, they are more stable in blood or plasma than are microRNAs (miRNAs) and long noncoding RNAs (lncRNAs).³ CircRNAs acting as "miRNA sponges" are involved in the initiation and progression of several types of cancer by binding to miRNAs.⁴ Moreover, recent studies have revealed that some circRNAs play significant roles in various kinds of cancer, including gastric cancer (GC), hepatocellular carcinoma (HCC), breast cancer (BC), colorectal cancer (CRC), and lung adenocarcinoma (LAC), among others.⁵ These findings

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However, due to small sample sizes and study design limitations, research evidence for the diagnostic accuracy of circRNAs in cancer is inaccurate and inadequate. To address these shortcomings, we conducted a comprehensive systematic analysis of data from all relevant publications to investigate the relationship between circRNAs and cancer diagnosis.

Methods

Literature search strategy

All potential literature in this meta-analysis was independently retrieved and screened by two researchers (GL and LS). A comprehensive and systematic search was conducted of the PubMed, Web of Science, Cochrane Library, Embase, CNKI, and IEEE online databases to identify eligible studies indexed through November 25, 2018. The search terms were as follows: "circular RNAs OR circRNAs" AND "cancer OR carcinoma OR tumor OR neoplasm" AND "sensitivity OR specificity OR ROC curve OR AUC OR diagnosis". In addition, the reference lists of the included articles were manually reviewed to identify additional relevant studies. As this study was based on previously published studies, no ethical approval or patient consent was required.

Selection criteria of reported research

The selection process in this meta-analysis was executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁶ All eligible studies fulfilled the following inclusion criteria. 1) Studies had a definite diagnosis of human cancer made using circRNAs. 2) All cancer cases were confirmed by pathological examination. 3) CircRNAs expression was detected in serum, plasma, or cancer tissue with quantitative reverse transcription-polymerase chain reaction (qRT-PCR) or other methods. 4) Studies provided sufficient diagnostic parameters to calculate true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN). The exclusion criteria included the following: 1) studies that did not satisfy the abovementioned inclusion criteria; 2) studies that were duplicate articles, reviews, animal studies, editorials, case reports, comments, and meta-analyses; 3) studies lacking sufficient data to construct a diagnostic 2×2 table.

Data extraction and quality assessment

Two researchers (GL and TH) carefully reviewed the full texts of all eligible studies and independently extracted the

relevant data, including the first author's name, publication year, country, cancer type, circRNA profiles, specimen, detection method, sample size, cutoff values, area under the curve (AUC), sensitivity and specificity, etc. Furthermore, 2×2 tables were created using TP, FP, TN, and FN. Any disagreement among the authors was resolved through discussions with a third author (LS) until a consensus was reached.

Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used to appraise the risk of bias and applicability of the included studies using Review Manager 5.2 software.⁷ The QUADAS-2 tool consists of four key domains: patient selection, index test, reference standard, and flow and timing. The risk of bias and concerns regarding applicability were evaluated as "low", "high", or "unclear".

Statistical analysis

Statistical analysis of the diagnostic tests was executed using Stata 14.0, Meta-DiSc 1.4, and Review Manager 5.2. Q tests and I^2 statistics were used to estimate the heterogeneity caused by a non-threshold effect among the included articles. Either P < 0.10 or $I^2 > 50\%$ suggested the existence of substantial heterogeneity; in this study, a random-effects model was applied to quantify the pooled sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and AUC, with corresponding 95% confidence intervals (CIs). Otherwise, a fixed-effects model was used. Spearman correlation analysis was conducted to verify the threshold effects. Moreover, subgroup analysis and metaregression were applied to trace the sources of heterogeneity. Sensitivity analysis was performed to assess the stability of our analysis. Publication bias was evaluated with Deeks' funnel plots. All tests were two-sided and P<0.05 was considered statistically significant.

Results

Literature search and selection of studies

A total of 290 articles were systematically retrieved from the online databases. A total of 231 records remained after duplicates were removed. First, we roughly screened the titles and abstracts and eliminated 161 publications that were irrelevant to the topic. The remaining 70 articles were further examined by careful review of the full text; as a result, 46 articles were excluded. Finally, a total of 32 eligible studies from 24 articles⁸⁻³¹ involving 3,016 participants were included in the meta-analysis. The flow diagram is shown in Figure 1.



Figure I Flow diagram of the study selection process.

Study characteristics

The main characteristics of the studies are listed in Table 1. This diagnostic meta-analysis analyzed 32 eligible studies from 24 articles involving 2,400 cases and 2,295 controls. All cancer cases were confirmed pathologically and the controls consisted of adjacent nontumorous tissue, noncancer tissue, or plasma from unaffected subjects. Specifically, tissue, plasma or saliva specimens were collected before treatment including radiotherapy, chemotherapy, and targeted therapy. The expression of circRNAs was detected by qRT–PCR. All studies referred to five different cancer types: gastric (GC, n=16), liver (HCC, n=7), breast (BC, n=3), colorectal (CRC, n=3), lung (LAC, n=2), and oral squamous cell carcinoma (OSCC, n=1).

Quality assessment

A quality assessment of the eligible studies was performed using QUADAS-2 (Figure 2). The figure depicts the relatively moderate quality of the 32 included studies. Most studies had either low or unclear risks of bias due to a lack of information on patient selection, exclusion criteria, or pre-specified thresholds.

Diagnostic accuracy

Heterogeneity among studies was evaluated by examining the threshold and non-threshold effects. In our study, the Spearman correlation coefficient and *P*-value were 0.658 and 0.218, respectively, suggesting that there was no threshold effect. Heterogeneity owing to non-threshold effects was then assessed with *Q*-tests and l^2 statistics.

| Author | Year | circRNAs profiles | Cancer type | Specimen | Test method | Sample size (case/ control) | Sensitivity | Specificity |
|----------------------------|------|--|----------------|----------------------------|-------------------------------|-----------------------------------|-------------------------|-------------------------|
| Li et al. ⁸ | 2017 | hsa_circ_0000096 | GC | Tissues | qRT-PCR | 101/101 | 0.880 | 0.560 |
| Zhu et al. ⁹ | 2017 | hsa_circ_0013958 hsa_circ_0013958 | LAC LAC | Tissues Plasma | qRT–PCR qRT–PCR | 49/49 30/30 | 0.755 0.667 | 0.796 0.933 |
| Yin et al. ¹⁰ | 2017 | hsa_circ_0001785 hsa_circ_0108942 hsa_circ_0068033 | BC BC BC | Plasma Plasma Plasma | qRT-PCR qRT-PCR qRT-PCR | 20/20 20/20 20/20 | 0.786 0.815 0.732 | 0.756 0.504 0.578 |
| Zhao et al. ¹¹ | 2017 | hsa_circ_0000181 hsa_circ_0000181 | GC GC | Tissues Plasma | qRT–PCR qRT–PCR | 115/115 102/105 | 0.539 0.990 | 0.852 0.206 |
| Fu et al. ¹² | 2017 | hsa_circ_0003570 | нсс | Tissues | qRT-PCR | 107/107 | 0.449 | 0.868 |
| Li et al. ¹³ | 2017 | hsa circ 0001649 | GC | Tissues | qRT-PCR | 76/76 | 0.711 | 0.816 |
| Qin et al. ¹⁴ | 2015 | hsa_circ_0001649 | нсс | Tissues | qRT-PCR | 89/89 | 0.810 | 0.690 |
| Wang et al. ¹⁵ | 2015 | hsa_circ_001988 | CRC | Tissues | qRT-PCR | 31/31 | 0.680 | 0.730 |
| Yao et al. ¹⁶ | 2017 | circZKSCANI | нсс | Tissues | qRT-PCR | 102/102 | 0.822 | 0.724 |
| Zhuo et al. ¹⁷ | 2017 | circRNA0003906 | CRC | Tissues | qRT-PCR | 122/40 | 0.725 | 0.803 |
| Li et al. ¹⁸ | 2017 | hsa_circ_0001017 hsa_circ_0061276 | GC GC | Plasma Plasma | qRT–PCR qRT–PCR | 2 / 2 2 / 2 | 0.974 0.903 | 0.811 0.517 |
| Shang et al. ¹⁹ | 2016 | hsa_circ_0005075 | нсс | Tissues | qRT-PCR | 30/30 | 0.833 | 0.900 |
| Li et al. ²⁰ | 2015 | hsa_circ_002059 | GC | Tissues | qRT-PCR | 101/101 | 0.810 | 0.620 |
| Chen et al. ²¹ | 2017 | hsa_circ_0000190 hsa_circ_0000190 | GC GC | Tissues Plasma | qRT–PCR qRT–PCR | 104/104 104/104 | 0.721 0.414 | 0.683 0.875 |
| Huang et al. ²² | 2017 | hsa_circ_0000745 | GC | Plasma | qRT-PCR | 60/60 | 0.855 | 0.450 |
| Lu et al. ²³ | 2017 | hsa_circ_0006633 | GC | Tissues | qRT-PCR | 96/96 | 0.600 | 0.810 |
| Sun et al. ²⁴ | 2017 | hsa_circ_0000520 | GC | Tissues | qRT-PCR | 56/56 | 0.536 | 0.857 |
| Tian et al. ²⁵ | 2017 | hsa_circ_0000521 hsa_circ_0003159 | GC GC | Plasma Tissues | qRT–PCR qRT–PCR | 45/17 108/108 | 0.824 0.852 | 0.844 0.565 |
| Lu et al. ²⁶ | 2018 | hsa_circ_0000467 | GC | Plasma | qRT-PCR | 20/20 | 0.705 | 0.648 |
| Zhang et al. ²⁷ | 2018 | hsa_circ_0091579 hsa_circ_16245-1 | нсс нсс | Tissues Tissues | qRT–PCR qRT–PCR | 30/30 30/30 | 0.970 0.830 | 0.400 0.630 |
| Shao et al. ²⁸ | 2017 | hsa_circ_0001895 | GC | Tissues | qRT-PCR | 96/96 | 0.678 | 0.857 |
| Wang et al. ²⁹ | 2017 | hsa_circ_0000567 | CRC | Tissues | qRT-PCR | 102/102 | 0.833 | 0.765 |
| Zhao et al. ³⁰ | 2018 | hsa_circ_0081001 | oscc | Salivary | qRT-PCR | 90/82 | 0.744 | 0.902 |
| Fu,et al. ³¹ | 2017 | hsa_circ_0004018 | нсс | Tissues | qRT-PCR | 102/102 | 0.716 | 0.815 |

| Table | L | Main | characteristics | of | the | studies | included | in | the | meta-anal | vsis |
|-------|---|------|-----------------|------|-----|---------|----------|----|-----|-----------|------|
| | - | | | •••• | | | | | | annan | / |

Abbreviations: GC, gastric cancer; BC, breast cancer; HCC, hepatocellular carcinoma; CRC, colorectal cancer; LAC, lung adenocarcinoma; OSCC, oral squamous cell carcinoma; qRT-PCR, quantitative reverse transcription PCR.



Figure 2 Quality assessment of the included studies according to QUADAS-2.



Figure 3 Forest plots of sensitivity and specificity of circRNAs for cancer diagnosis. (A) Pooled sensitivity for circRNAs. (B) Pooled specificity for circRNAs.

There was significant heterogeneity in the pooled sensitivity (I^2 =89.57%, P<0.001) and specificity (I^2 =90.88%, P<0.001); thus, a random-effects model was applied to analyze the diagnostic parameters. The pooled sensitivity and specificity were 0.79 (95% CI: 0.73–0.84) and 0.73 (95% CI: 0.67–0.79), respectively (Figure 3). In addition, the pooled PLR, NLR, and DOR were 2.9 (95% CI: 2.5–3.5), 0.29 (95% CI: 0.24–0.36), and 10 (95% CI:

8–13), respectively. The summary receiver operator characteristic (SROC) curve is shown in Figure 4; the AUC was 0.83. These results indicated that circRNAs have potential diagnostic value for several cancers.

Subgroup analysis and meta-regression

To explore the potential sources of heterogeneity, subgroup analyses were first performed based on specimen (tissue vs



Figure 4 Summary receiver operator characteristic curve for cancer diagnosis.

other), case size (≥ 100 vs <100), and cancer type (GC vs other) (Table 2). Studies using other samples (plasma or saliva) had better diagnostic accuracy than those using tissue samples for cancer diagnosis, with increased sensitivity (0.75 vs 0.84), decreased NLR (0.33 vs 0.23), increased DOR (9 vs 12), and increased AUC (0.81 vs 0.84). Additionally, studies involving ≥ 100 cases or GC showed higher sensitivities but lower specificities than those involving <100 cases or other cancers. However, meta-regression analyses indicated that no methodological covariates affected the diagnostic accuracy of circRNAs (all joint *P*>0.05).

| Table 2 Results | of | subgroup | analysis |
|-----------------|----|----------|----------|
|-----------------|----|----------|----------|

We also analyzed subgroups according to cancer type, and the main results were summarized in Figure 5. Significant heterogeneity was observed in the GC group $(I^2=57.8\%, P=0.002)$. No significant heterogeneity was observed in the HCC $(I^2=23.0\%, P=0.254)$, CRC $(I^2=13.9\%, P=0.313)$, LAC $(I^2=0.0\%, P=0.379)$, and BC $(I^2=0.0\%, P=0.517)$ subgroups. The results suggest that cancer type may act as potential sources of heterogeneity.

Sensitivity analysis

To further explain the heterogeneity of individual studies, we performed a sensitivity analysis by removing individual studies. As shown in Figure 6, no outlier study was identified and the results were relatively stable and reliable.

Publication bias

Deeks' funnel plot asymmetry tests were applied to estimate publication bias in the meta-analysis (shown in Figure 7). The results confirmed the lack of significant publication bias across the overall combined diagnostic studies (P=0.68, >0.05).

Discussion

Owing to their closed continuous loop structure, circRNAs are more stable in the extracellular space compared to linear RNAs. This feature makes circRNAs advantageous for use as molecular markers of cancer. The current study comprehensively assessed the diagnostic efficacy of circRNAs for several cancers. The pooled effect showed the relatively high level of diagnostic accuracy of circRNAs, suggesting their potential as effective biomarkers for cancer diagnosis.

| Subgroups | Studies | Sensitivity [95% Cl] | Specificity [95% Cl] | PLR [95% CI] | NLR [95% CI] | DOR [95% CI] | AUC [95% CI] |
|-------------|---------|-------------------------|-------------------------|-----------------|-----------------|-----------------|-----------------|
| Specimen | | | | | | | |
| Tissue | 20 | 0.75[0.69–0.80] | 0.75[0.69–0.80] | 3.0[2.6–3.5] | 0.33[0.28–0.40] | 9[7–11] | 0.81[0.78–0.85] |
| Other | 12 | 0.84[0.72–0.91] | 0.70[0.56–0.82] | 2.8[1.9-4.2] | 0.23[0.14–0.38] | 12[7–23] | 0.84[0.81–0.87] |
| Case size | | | | | | | |
| ≥100 | 17 | 0.82[0.72-0.89] | 0.70[0.61-0.78] | 2.8[2.2–3.5] | 0.25[0.17-0.37] | 11[8–16] | 0.82[0.79–0.85] |
| <100 | 15 | 0.74[0.69–0.79] | 0.77[0.69–0.83] | 3.2[2.4-4.2] | 0.34[0.28–0.40] | 10[7–13] | 0.81[0.77–0.84] |
| Cancer type | | | | | | | |
| GC | 16 | 0.80[0.69–0.87] | 0.71[0.61-0.79] | 2.7[2.1–3.5] | 0.29[0.20-0.41] | 9[6–14] | 0.81[0.78-0.85] |
| Other | 16 | 0.78[0.71–0.83] | 0.76[0.70–0.82] | 3.3[2.6-4.0] | 0.29[0.24–0.37] | [8- 5] | 0.84[0.80–0.87] |
| Overall | 32 | 0.79[0.73–0.84] | 0.73[0.67–0.79] | 2.9[2.5–3.5] | 0.29[0.24–0.36] | 10[8–13] | 0.83[0.79–0.86] |

Abbreviations: GC, gastric cancer; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odd ratio; AUC, area under the curve.

| GC UP 2017 2.85 (4.85, 19.73) 4.00 Zheo Q(g) 2017 UP 2017 4.64 (5.9, 19.73) 4.00 Zheo Q(g) 2017 UP 2017 2.85 (4.85, 19.73) 4.00 UP 2017 Description 2.46 (4.85, 19.73) 4.00 UP 2017 Description 2.86 (4.85, 19.73) 4.00 UP 2017 Description 2.86 (4.85, 19.73) 4.80 UP 2017 Description 4.44 2.86 (4.85, 19.73) 4.80 UP 2016 Statistic (4.81, 19.70) 4.81 2.85 (6.00, 27.95) 4.46 UP 2017 Statistic (4.81, 17.10) 3.31 3.80 1.81 2.85 (5.00, 37.106) 4.61 UP 2017 Statistic (4.88, 17.43) 1.34 2.95 (5.00, 37.106) 4.21 2.35 3.31 3.32 Shan H0 2017 Statistic (4.88, 14.34) 4.44 1.44 1.44 1.45 1.32 2.31 (5.15, 16.20) 3.31 1.22 (6.04, 24.86) 4.21 UP 2017 Statistic (4.92, 19.81, 17) 2.33 (6.31, 24.90) 3.32 2.33 (6.31, 24.90) 3 | Study ID | OR (95% CI) | Weight % |
|---|--|--|----------|
| Li P 2017 Zhao C(a) 2017 Zhao C(a) 2017 Li W 2017 Li R 2017 San H(a) 2017 San H(a) 2017 Li R 2017 San H(a) 2017 San H(a) 2017 Li R 2017 San H(a) 2017 Hung X 2016 Zhang C(a) 2018 Zhang C(a) 2018 | GC | <u>_i</u> | |
| Zhao Q(a) 2017 6.74 (3.58, 12.69) 4.46 LW 2017 10.67 (507, 23.31) 3.79 L T(a) 2017 10.67 (507, 23.31) 3.79 L T(a) 2017 10.68 (59, 20.68) 2.15 L P 2015 5.87 (4.58, 19.76) 4.13 L P 2016 5.987 (4.58, 19.76) 4.13 L P 2017 4.39 (2.45, 9.84) 4.10 L R 2017 4.39 (2.45, 9.84) 4.10 Sun Hiuj 2017 4.39 (2.45, 9.84) 4.30 Lu R 2017 6.61 (3.4, 12.74) 4.33 Sun Hiuj 2017 2.15 (5.00, 9.317) 1.67 Sun Hiuj 2017 2.15 (5.00, 9.317) 1.67 Sun Hiuj 2017 2.13 (5.1, 12.69) 4.31 Sun Hiuj 2017 2.13 (5.1, 12.69) 4.31 Sun Hiuj 2017 2.13 (5.1, 12.69) 4.31 Shara X 2016 2.17 1.12 (2.16, 0.41, 13.59) 5.45 Shara X 2016 2.17 1.13 (1.57, 12.59) 2.54 Subbolal (lexquared = 2.30%, p = 0.254) 1.10 (0.66, 2.12.0) 4.32 Vin Witoy 2017 1.00 (2.66, 2.12.0) 4.32 4.52 Yin Witoy 2017 | Li P 2017 | 9.61 (4.68, 19.73) | 4.00 |
| Zase G(b) 2017 266 4(5.5, 200.67) 0.58 U W2017 107 (60.2, 23.1) 3.79 U T(b) 2017 107 (50) (458, 574.86) 2.16 L T(b) 2017 566 (30.7, 10.69) 4.61 L T(b) 2017 566 (30.7, 10.69) 4.61 L T(b) 2017 566 (30.7, 10.69) 4.61 L R 2017 641 (34.1, 12.9) 3.31 Sun H(b) 2017 643 (34.2, 49.8) 4.10 L R 2017 643 (34.1, 27.9) 3.41 Sun H(b) 2017 12.8 (6.0, 20.17) 1.67 Subblal (I-squared = 57.8%, p = 0.02) 540 (27.4, 10.66) 4.21 Van X 2016 2.14 1.23 (3.1, 40.9) 4.38 Zhang C(a) 2018 540 (27.4, 10.66) 4.21 Yan X 2016 2.14 1.10 (66.9, 21.24) 4.32 Zhang C(a) 2018 1.10 (20.66.2, 14.9.1) 1.58 Zhang C(a) 2018 1.10 (20.66.2, 14.9.1) 1.20 (2.70, 53.33) 1.62 Yun W(b) | Zhao Q(a) 2017 | 6.74 (3.58, 12.69) | 4.46 |
| Li W 2017 Li W 2017 Li T(a) 2017 Li T(a) 2017 Li T(a) 2017 Li P 2013 Li P 2015 Li P 2015 Li P 2015 Li P 2016 Li P 2017 Li P 2017 Li P 2017 Li R 2017 Tam M 2017 Tam M 2017 Tam M 2017 Tam M 2017 Tam M 2017 Tam M 2017 Li P 2017 Ci P 2017 Li P | Zhao Q(b) 2017 | 26.64 (3.53, 200.87) | 0.98 |
| Li Tig) 2017 Li Tig) 2017 Li Tig) 2017 Li Tig) 2017 Li P 2015 Chen S(p) 2017 Li P 2015 Chen S(p) 2017 Li P 2018 Li P 2017 Li P 2016 Li P 2017 Li P 2016 Li P 2016 Li P 2016 Li P 2016 Li P 2017 Li P 2016 Li P 2016 Li P 2017 Li P 2016 Li P 2016 Li P 2017 Li P 2016 Li P 2017 Li P 2016 Li P 2017 Li P 2016 Li P 2017 Li P 2017 | Li W 2017 | 10.87 (5.07, 23.31) | 3.79 |
| Li Tub 2017 Li Tub 2017 Li P 2015 Chen S(a) 2017 Chen S(a) 2018 Chen S(a) 2018 Chen S(a) 2018 Chen S(a) 2018 Chen S(a) 2018 Chen S(a) 2017 Chen S(a) 2018 Chen S(a) 2017 Chen S(a) 2018 Chen S(a) 2018 Chen S(a) 2017 Chen S(a) 2018 Chen S(a) 2018 Chen S(a) 2018 Chen S(a) 2017 Chen S(a) 2018 Chen S(a) 2017 Chen S(a) 2018 Chen S(a) 2017 Chen S(a) | Li T(a) 2017 | 1 1 1 6 7 1 1 6 7 1 1 1 1 1 1 1 1 1 1 | 2.15 |
| LP 2015 Chen S(a) 2017 Chen S(b) 2017 Huang M 2017 LIR 2017 Sun H(b) 2017 Tan M 2017 CRC Wang X 2015 Zhang C(a) 218 Subtolal (I-squared = 57.8%, p = 0.002) CRC Wang X 2015 Zhang C(a) 218 Subtolal (I-squared = 13.9%, p = 0.254) CRC Wang X 2015 Zhang C(a) 217 Tyn W(a) 2017 Tyn W(b) 2017 Tyn W | Li T(b) 2017 | 9.87 (4.93, 19.76) | 4.13 |
| Chen S(b) 2017 Chen S(b) 2017 Hang M 2017 Lu R 2017 Sun H(a) 2017 Tian M 2017 Lu R 2017 Sun H(a) 2017 Tian M 2017 Lu 7201 Subbolal (Lequared = 57.8%, p = 0.002) HCC FL 2017 Cin M 2015 Subbolal (Lequared = 57.8%, p = 0.002) HCC FL 2017 Cin M 2015 Subbolal (Lequared = 57.8%, p = 0.002) HCC FL 2017 Cin M 2015 Subbolal (Lequared = 57.8%, p = 0.002) HCC FL 2017 Cin M 2015 Subbolal (Lequared = 57.8%, p = 0.002) HCC FL 2017 Cin M 2015 Subbolal (Lequared = 13.9%, p = 0.254) FL 2017 Cin M 2015 Subbolal (Lequared = 13.9%, p = 0.254) FL Co FL 2017 Cin M 2015 Subbolal (Lequared = 13.9%, p = 0.254) FL Co FL 2017 Cin M 2015 Subbolal (Lequared = 0.0%, p = 0.517) FL Co Tin W(a) 2017 Subbolal (Lequared = 0.0%, p = 0.517) FL Co Tin W(a) 2017 Subbolal (Lequared = 0.0%, p = 0.517) FL Co Cin M 2017 Subbolal (Lequared = 0.0%, p = 0.517) FL Co Tin W(a) 2017 Subbolal (Lequared = 0.0%, p = 0.517) FL Co Tin W(a) 2017 Subbolal (Lequared = 0.0%, p = 0.517) FL Co Tin W(a) 2017 Subbolal (Lequared = 0.0%, p = 0.517) FL Co Tin W(a) 2017 Subbolal (Lequared = 0.0%, p = 0.517) FLC Tin W(a) 2017 Subbolal (Lequared = 1.74,4%, p = 0.002) FLC Tin W(a) 2017 Subbolal (Lequared = -0.0%, p = 0.517) FLC Tin W(a) 2017 Subbolal (Lequared = -0.0%, p = 0.517) FLC Tin W(a) 2017 Subbolal (Lequared = -0.0%, p = 0.517) FLC FLC Tin W(a) 2017 Subbolal (Lequared = -0.0%, p = 0.517) FLC FLC FLC FLC FLC FLC FLC FLC | Li P 2015 | 7.16 (3.77, 13.59) | 4.41 |
| Chen S(b) 2017 Huang M 2017 LR 2017 Sun H(b) 2017 Tian M 2017 La 2018 Subblati (Lequared = 57.8%, p = 0.002) HCC FUL 2017 CMC Wang X 2016 Zhang C(a) 2018 Subblati (Lequared = 13.9%, p = 0.254) LCC Thu K(b) 2017 Yin W(a) 2017 Yin W(b) 2017 Yin Y | Chen S(a) 2017 | 5.56 (3.07, 10.09) | 4.66 |
| Huang 2017 Lu R 2017 Sun H(a) 2017 Sun H(a) 2017 Sun H(a) 2017 Sun H(a) 2017 Sun H(a) 2017 Sun H(a) 2017 Tria M 2017 Subtall (requared = 57.8%, p = 0.002) HCC Fu L 2017 Fu L 2 | Chen S(b) 2017 - | 4.93 (2.45, 9.94) | 4.10 |
| Lu R 2017 Sun H(g) 2017 Tian M 2017 Tian M 2017 Lu 2018 Shao Y 2017 Subtotal (I-squared = 57.8%, p = 0.002) HCC Fu L 2017 Oli M 2015 Subtotal (I-squared = 57.8%, p = 0.002) HCC Fu L 2017 Oli M 2015 Sharg X 2016 Zhang C(g) 2018 Sharg X 2016 Zhang C(g) 2018 Fu L(b) 2017 Wang X 2015 Zhang C(g) 2017 Subtotal (I-squared = 3.9%, p = 0.313) - CRC Wang X 2017 Zhang C(g) 2017 Yin W(g) 2017 Yin W(g) 2017 Zhang C(g) 2017 Zhang C(g) 2017 Subtotal (I-squared = 0.0%, p = 0.317) - CC Zha S 2018 Subtotal (I-squared = 0.0%, p = 0.379) - CC Zha S 2018 Subtotal (I-squared = 47.4%, p = 0.002) NOTE: Weights are from random effects analysis - Data - CC CC CC CC CC CC CC CC CC C | Huang M 2017 - | 4.64 (1.94, 11.09) | 3.31 |
| Sun H(b) 2017 Sun H(b) 2017 Tan M 2017 Lu J 2018 Subtotal (1-squared = 57.8%, p = 0.002) HCC Fu L 2017 Clim M 2015 Yan Z 2017 Zhang C(a) 2018 Zhang C(a) 2018 Zhang C(a) 2018 CRC Yin W(b) 2017 Yin W(c) 2017 Yin W(c) 2017 Yin W(c) 2017 Yin W(c) 2017 Yin W(c) 2017 Zhu S 2018 CC Tu L 2017 CRC Yin W(c) 2017 Yin Yin Yin Yin Yin Yin Yin Yin Yin Yin | Lu R 2017 | 6.61 (3.43, 12.74) | 4.33 |
| Sun H(b) 2017 Tian M 2017 Lu J 2018 Shao Y 2017 Subtolal (I-squared = 57.8%, p = 0.002) HCC FUL 2017 Cin M 2015 Yan Q(b) 2018 Shang X 2015 Shang X 2016 Chang C(c) 2018 Shang X 2015 Shang X 2016 Chang C(c) 2018 Shang X 2015 CRC Wang X 2015 Wang X 2015 Wang X 2015 CRC Wang X 2015 Wang X 2015 CRC Wang X 2015 Wang X 2015 CRC Wang X 2015 CRC CRC CRC CRC CRC CRC CRC CR | Sun H(a) 2017 | 6.92 (2.77, 17.27) | 3.14 |
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Figure 5 Subgroup analyses according to cancer type.



Figure 6 Sensitivity analysis of the overall pooled study.



Figure 7 Deeks' funnel plot to assess publication bias. Abbreviation: ESS, effective sample size.

CircRNAs have recently been identified as a family of naturally occurring endogenous noncoding RNAs that may regulate gene expression in mammals.³² With the widespread application of bioinformatics and next-generation

sequencing technologies, a large number of circRNAs have been sequenced and entered into a database of 32,914 human exonic circRNAs.³³ In addition, some circRNAs are related to cancer diagnosis. Previous studies

have shown that circRNAs play a crucial role in transcriptional or posttranscriptional regulation of gene expression.³⁴ Moreover, circRNAs, acting as efficient microRNA (miRNA) sponges, can specifically bind to miRNAs and compete with endogenous RNA, strongly suppressing microRNA activity and potentially contributing to tumor progression.³ Furthermore, circRNAs are associated with RNA binding proteins, which play crucial roles in cancer development through dysregulation of transcription or expression.35 Most importantly, circRNAs are more abundant and stable than the corresponding linear RNAs. Recently, a fusion circRNA (F-circEA) was discovered to monitor fusion genes involved in tumorigenesis, which could be a potential novel "liquid biopsy" biomarker in nonsmall cell lung cancer.³⁶ Li et al first reported on exosomes enriched with stable circRNAs and proposed their potential of circRNAs as a new class of cancer biomarkers.³⁷ These findings suggest that circRNAs may be a promising diagnostic biomarker for cancer.

Our study, comprising 3,016 participants (2,400 cases and 2,295 controls) is the most comprehensive metaanalysis to assess the diagnostic value of circRNAs for various cancers. Two meta-analyses have been published on the diagnostic value of circRNAs. Li et al³⁸ and Wang et al³⁹ reported circRNA AUCs of 0.793 and 0.79, respectively. Compared to their results, our study observed a higher diagnostic efficiency (AUC=0.83). In our meta-analysis, we first conducted a quality assessment of the 32 enrolled studies, which revealed relatively moderate quality. The overall pooled sensitivity, specificity, and AUC of circRNAs for cancer diagnosis were 0.79 (95% CI: 0.73-0.84), 0.73 (95% CI: 0.67-0.79), and 0.83 (95% CI: 0.79-0.86), respectively; higher values than those for traditional plasma-based biomarkers such as CEA and CA19-9.40 In addition, the pooled DOR of circRNAs was 10, suggesting a powerful discriminating capacity of circRNAs for cancer diagnosis. Together, these findings suggest that circRNAs might be effective biomarkers for cancer diagnosis.

The pooled results indicated that there was significant heterogeneity that could impact the accuracy among the overall studies. The Spearman correlation coefficient was $0.658 \ (P=0.218)$, suggesting that the threshold effect was not the source of heterogeneity. We further performed meta-regression and subgroup analysis. Studies with plasma samples had better diagnostic accuracy, while ≥ 100 cases or GC showed higher sensitivities than those with <100 cases or other cancers. The results implied that specimen, case size, and cancer type might influence the diagnostic accuracy; however, the differences were not statistically significant. Sensitivity analysis was also conducted to analyze the heterogeneity, but no outlier studies were found. The heterogeneity could derive from confounding factors and differences in methodology.

The present meta-analysis has several limitations. First, there was significant heterogeneity among the included studies. Although we performed subgroup analysis and meta-regression to explore the sources of heterogeneity, the results did not fully explain the potential heterogeneity. Second, only studies conducted in Asia were included; therefore, the results for other ethnicities might be missed, which may lead to population selection bias. Therefore, additional higher-quality, multicenter, and well-designed studies are required to confirm our findings.

Conclusion

The results of our meta-analysis suggest the potential of circRNAs as biomarkers for the diagnosis of several cancers, with good diagnostic efficiency (AUC=0.83). However, the application of circRNAs for cancer diagnosis requires further validation.

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Disclosure

The authors report no conflicts of interest in this work.

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