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Diagnostic Accuracy of CircRNAs for Detecting Gastrointestinal Cancers: An Updated Meta-analysis

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Abstract

Background: Gastrointestinal (GI) cancers remain a leading cause of cancer-related mortality worldwide, underscoring the urgent need for reliable, non-invasive diagnostic biomarkers. Circular RNAs (circRNAs), characterized by high stability and tissue specificity, have emerged as promising molecular indicators for early cancer detection. This study aimed to evaluate the diagnostic accuracy of circular RNAs (circRNAs) for detecting gastrointestinal (GI) cancers, including gastric cancer (GC), hepatocellular carcinoma (HCC), esophageal cancer (EC), colorectal cancer (CRC), and pancreatic cancer (PC).

Methods: A comprehensive literature search was conducted in PubMed, Web of Science, Scopus, and EMBASE up to December 2024, following PRISMA guidelines. Quality assessment was performed using the QUADAS-2 tool. Diagnostic accuracy metrics were analyzed using Metandi and Midas modules in STATA 17.

Results: From 9,733 retrieved articles, 139 studies involving 25,847 participants and 153 circRNAs met inclusion/exclusion criteria. No new eligible studies were identified from July 2021 to December 2024. The pooled diagnostic performance of circRNAs for gastrointestinal cancers was: sensitivity 0.78 (95% CI: 0.76–0.79), specificity 0.76 (95% CI: 0.74–0.77), PLR 3.3 (95% CI: 3.1–3.5), NLR 0.29 (95% CI: 0.27–0.31), and AUC 0.83 (95% CI: 0.80–0.85). Specific circRNAs (e.g., hsa_circ_0001017, circ-SLC7A5, circ-LDLRAD3) showed promising diagnostic performance.

Conclusion: CircRNAs exhibit good diagnostic accuracy for hepatocellular carcinoma (AUC 0.83) and esophageal cancer (AUC 0.81), moderate-to-good accuracy for gastric cancer (AUC 0.79) and pancreatic cancer (AUC 0.78), but limited accuracy for colorectal cancer (AUC 0.68), highlighting their potential as non-invasive biomarkers, particularly for HCC and EC, with further validation needed to enhance clinical utility.

Keywords: Gastrointestinal cancers, circRNAs, Biomarkers, Diagnostic accuracy, Meta-analysis

Conflicts of Interest: *None declared*
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Introduction

Gastrointestinal (GI) cancers refer to malignant conditions of the GI tract and related digestive organs. The most common types include gastric cancer (GC), hepatocellular carcinoma (HCC), esophageal cancer (EC), colorectal cancer (CRC), and pancreatic cancer (PC). Together, GI cancers account for nearly 35% of all cancer-related deaths and

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↑What is "already known" in this topic:
Circular RNAs (circRNAs) have emerged as promising biomarkers for cancer detection, with multiple studies suggesting their diagnostic potential in gastrointestinal (GI) malignancies. However, the current evidence remains fragmented and lacks comprehensive pooled estimates across different cancer types.

→What this article adds:
This meta-analysis integrates findings from 139 studies evaluating 153 circRNAs in more than 25,000 participants, providing robust pooled diagnostic metrics. It demonstrates strong diagnostic accuracy for hepatocellular and esophageal cancers, moderate performance for gastric and pancreatic cancers, and limited accuracy for colorectal cancer. These results support circRNAs as non-invasive biomarkers and establish a foundation for future multicenter validation and clinical application.

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26% of the global cancer incidence burden, with an estimated 4.8 million new cases and 3.4 million deaths worldwide in 2018 (1).

Circular RNAs (circRNAs) are a type of closed, long non-coding RNA that regulates diverse biological processes, including cancer development. They are abundant, structurally stable, and often expressed in a cell type– or tissue-specific manner (2). CircRNAs participate in oncogenic pathways by acting as microRNA sponges or recruiting RNA-binding proteins to influence protein translation. These roles suggest both oncogenic and tumor-suppressive functions (3, 4). In GI cancers, circRNAs have been associated with tumor size (5), disease stage (6), and overall survival (7), which introduces them as potential biomarkers (8, 9). Although many studies report circRNAs as promising biomarkers for GI cancers, findings are inconsistent. Diagnostic accuracy estimates vary widely by cancer type, specimen source, and circRNA expression level. A comprehensive synthesis is therefore necessary to clarify their diagnostic potential. Therefore, this study aimed to systematically evaluate the diagnostic accuracy of circRNAs across the five major gastrointestinal cancers (gastric, hepatocellular, esophageal, colorectal, and pancreatic) through an updated meta-analysis. By synthesizing available evidence, we sought to clarify their diagnostic potential, identify sources of heterogeneity, and assess their suitability as complementary clinical tools.

Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) (10).

Search Strategy and Screening

A comprehensive search was conducted in PubMed, Web of Science, Scopus, and EMBASE up to December 2024 to identify studies evaluating the diagnostic accuracy of circRNAs for GI cancers, following the search strategies outlined in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (10). We used Boolean logic operators for the development of the search strategy. We used all retrieved keywords from the MeSH database and Emtree for “gastrointestinal cancers” and “Circular RNA”. We also reviewed the references of all relevant studies to avoid missing any eligible articles (Manual Search). After removing duplicate studies, two independent reviewers (SN and ZB) performed a screening based on the titles and abstracts of the articles. Any disagreement between reviewers was discussed, and conflicts were resolved by a third researcher (YM). Also, in studies in which sensitivity and specificity were not directly mentioned and only had receiver operating characteristic (ROC) curves, their sensitivity and specificity were calculated separately by the two authors (SN and ZB) from the ROC curves, so that the highest and closest point to the axis of sensitivity was considered to calculate sensitivity and specificity and finally approved by a third party (KA). We conducted a PRISMA diagram to illustrate the study selection process (10).

Eligibility Criteria

Articles were included in this study when the following criteria were met: i. Case-control or cohort study, retrospective or prospective, cross-sectional study; ii. Patients diagnosed with GI cancers (Inner lining of the esophagus, stomach, and small intestine) based on guidelines (11) and/ or with an expert clinician; iii. Controls without GI cancers according to guidelines (11); iv. Studies should evaluate at least the level of one circRNA in serum/plasma/tissue; v. Studies restricted to the English language. All review articles, duplicated articles, non-peer-reviewed articles, book chapters, and letters were excluded. Also, the studies that were done on other species or animals instead of humans, studies rather than cohorts or case-control studies, and studies with insufficient data where true negatives (TN), true positives (TP), false negatives (FN), and false positives (FP) were not provided or could not be calculated indirectly were excluded. It should be noted that Esophagogastroduodenoscopy (EGD), along with biopsy, was considered a gold standard test for upper GI cancers (Inner lining of the esophagus, stomach, and small intestine). Also, the biopsy is the gold standard for diagnosing PC obtained by endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography (ERCP). Both computed tomography (CT) and magnetic resonance imaging (MRI) constitute the gold standard in radiological imaging of HCC. Colonoscopy was a gold standard test, and imaging methods like CT scans were considered standard tests for cancers in the lower GI tract. The biopsy is a method for confirmation of endoscopy and imaging results, which together are the gold standard for GI cancers.

Data extraction

The following items were collected from each article by ZB and SN, independently: publication year, country, the number of participants (patients and controls), sample source of circRNA, the name of circRNAs, expression level of circRNAs, type of GI cancer, target point of circRNAs, TP, TN, FP, and FN.

The TP, TN, FP, and FN data were extracted from the 2×2 table of studies or (if this table was not provided with studies) calculated using the specificity, sensitivity, and sample size of the patients and controls.

Quality Assessment

The methodological quality of the studies was assessed independently by two reviewers (ZB and SN) through the revised Quality Assessment Tool of the Diagnostic Accuracy Studies (QUADAS-2)(12), which was proposed for use by Cochrane to address bias and application-related concerns. The risk of bias by this tool is assessed by scoring questions in four domains as follows; 1) patient selection (the method of patient selection and the patients included) 2) index test (the test being studied and how it was conducted and interpreted) 3) reference standard (the reference standard test used and how it was conducted and interpreted) 4) flow and timing (the flow of patient inclusion and exclusion, testing procedure and the interval between tests). The classification of domains was high, low, or unclear, and disagreements were resolved by discussion with the

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third reviewer (YM).

Statistical Analysis

We used the Metandi and Midas modules in the STATA 17 (Stata Corporation, College Station, TX, USA) statistical software to perform all the analyses (13, 14). The pooled sensitivity, pooled specificity, pooled positive likelihood ratio (PLR), pooled negative likelihood ratio (NLR), and pooled diagnostic odds ratio (DOR) and their corresponding 95% confidence interval (95% CI) were calculated by using the bivariate mixed-effects regression model and the hierarchical summary ROC (HSROC) model (15, 16). Results were displayed graphically on forest plots and the HSROC curves. Heterogeneity between the included studies was assessed using Cochran's Q test and the inconsistency index (I^2), describing the percentage of total variation across studies due to heterogeneity rather than chance(17). A p-value ≤ 0.05 and an I^2 value $\geq 50\%$ would indicate substantial heterogeneity. The threshold effect was checked using Spearman's rho, and potential sources of heterogeneity were explored by meta-regression. We assessed publication bias using Deeks' funnel plot and considered a *P*-value < 0.1 in the Deeks' asymmetry test to indicate publication bias (18).

Results

Literature search and study selection

In total, 9733 articles (2029 from PubMed, 1186 from Scopus, and 6518 from Web of Science) were retrieved, and after duplicate removal, 4160 articles were included in screening by title step. After that, 3081 articles were removed in this step, and 1079 articles were included in screening by the abstract step. Finally,139 eligible studies were included (after screening by full-text step) in the present systematic review from 2013 to 2019. Figure 1 shows the process of literature search and study selection as a flow diagram based on the PRISMA-based flow chart. Significant heterogeneity was observed across most pooled analyses (I^2 > 70%). To explore potential sources, we performed subgroup and meta-regression analyses. These indicated that heterogeneity was partly explained by specimen type (plasma vs. tissue vs. serum), circRNA expression status (upregulated vs. downregulated), and study region. Notably, plasma-derived circRNAs showed higher pooled sensitivity and specificity than tissue-based ones, while upregulated circRNAs demonstrated stronger diagnostic performance than downregulated circRNAs.

The characteristics of the included studies

In total, 25847 participants (the entire sample size) were assessed in 139 included studies investigating the diagnostic performance of 153 circRNAs for GI cancers. The list of 153 circRNAs detected collectively in GI cancers was separately reported in Table 1. Based on sample types, 93 circRNAs were detected in the tissue samples, 11 circRNAs were detected in the serum, 23 circRNAs were detected in the plasma, and four circRNAs were detected in peripheral blood smear (PBS). Also, two circRNAs were detected in both tissue and serum, 16 circRNAs were detected in both tissue and plasma, and four circRNAs were detected in both tissue and PBS (Table 2).

Diagnostic accuracy of circRNAs for Gastric Cancer

The accuracy of 61 circRNAs for GC detection was investigated in 55 studies (Appendix Table A1). The highest sensitivity was related to Li, T, W/ 2018, which was 95% (19), and the lowest sensitivity was related to Li Z / 2019,

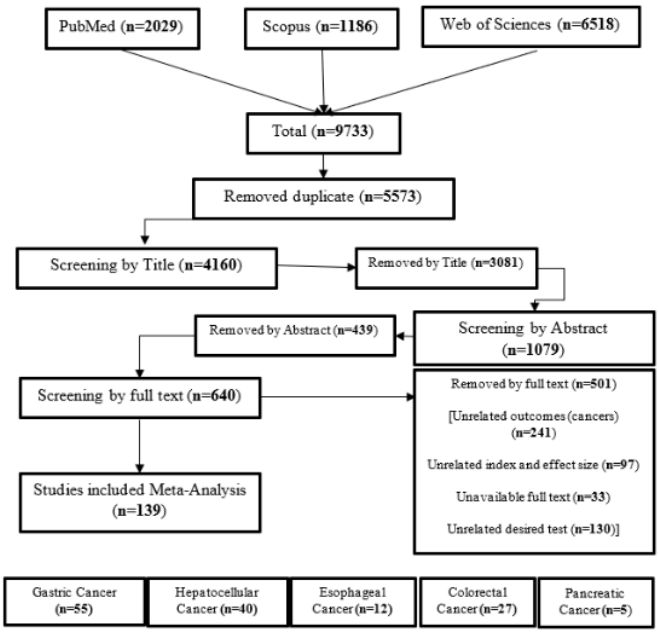

Figure 1. A flow diagram demonstrating the study selection process

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Table 1. List of circRNAs with the highest sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio

No.	circ-RNA	Type of cancer	Expression level	Target
1	hsa_circ_0001017	GC	Downregulation	3′-UTR region of RHOB gene (43)
2	hsa_cir c_0061276	GC	Downregulation	
3	hsa_circ_0001445	HCC	Downregulation	RNA-binding protein Quaking (QKI) (44)
4	circ-ADD3	HCC	Downregulation	EZH2 (45)
5	circ-0051443	HCC	Downregulation	BAK1 (46)
6	hsa_circ_0004277	HCC	Upregulation	HuR (47)
7	hsa_circ_0005397	HCC	Upregulation	unknown
8	circ-LRIG3 (hsa_circ_0027345)	HCC	Upregulation	EZH2-induced STAT3 Methylation (48)
9	Circ-SLC7A5	ES	Upregulation	bind to miRNAs (49)
10	hsa_circ_0043603	ES	Upregulation	bind to miRNAs (50)
11	circ-DLG1	ES	Upregulation	miR-942 and miR-630 (28)
12	circ-TTC17	ES	Upregulation	total of 20 microRNAs and corresponding target mRNAs (51)
13	circZNF609	CRC	Upregulation	Plasmids or naked RNA induce a non-specific block of myoblast proliferation (52)
14	circMBOAT2	CRC	Upregulation	sponging miR-519d-3p (53)
15	Hsa_circ_0002320	CRC	Downregulation	miRNAs (54)
16	circ-LDLRAD3	PC	Upregulation	unknown
17	hsa_circ_0000069	PC	Upregulation	SCL/TAL1 interrupting locus (55)
18	circEIF6	PC	Upregulation	miR-557/SLC7A11/PI3K/AKT (56)
19	hsa_circ_0071036	PC	Upregulation	sponging miR-489 (57)
20	circ_001569	PC	Upregulation	sponging miR-411-5p and miR-432-5p (58)

which was 21% (20). The highest specificity was related to Zhao, Q / 2018 (21), which was 98% and the lowest specificity was related to Shao, Y / 2020 (22). The overall and subgroup diagnostic ability of circRNAs for GC detection based on expression of circRNAs and sample sources is shown in Table 2. Result of meta-analysis show that the pooled of sensitivity, specificity, PLR, NLR, DOR, and accuracy circRNAs for GC detection was 71% (95% CI: 67%-75%), 75% (95% CI: 71%-79%), 2.9 (95% CI: 2.4-3.5), 0.39 (95% CI: 0.33-0.45), 7 (95% CI: 5-10), and 0.79 (95% CI: 0.75-0.82), respectively (Table 2 and Figure 2). Besides, the downregulation of two circRNAs, including hsa_circ_0001017 and hsa_cir c_0061276 was obtained as the most important biomarker for GC.

Diagnostic accuracy of circRNAs for Hepatocellular Carcinoma

From 40 included articles, the diagnostic accuracy of 46 circRNAs for HCC was extracted (Appendix Table A2). The highest sensitivity was related to Du, Q/2020, and Matboli, M/2019 (23, 24), which was 97% and the lowest sensitivity was related to Guan, Z / 2018, which was 27% (25). The highest specificity was related to Wang, W / 2020, which was 100% (26), and the lowest specificity was related to Liu, B/2020, which was 33% (27). Four sources of tissue, serum, plasma, and tissue & blood for HCC were examined. The overall and subgroup diagnostic ability of circRNAs for HCC detection based on expression of circRNAs and sample sources is shown in Table 2.

CircRNAs had an overall pooled sensitivity of 76% (95% CI: 70%-81%), a pooled specificity of 76% (95% CI: 71%-80%), and a pooled PLR of 3.2 (95% CI: 2.6-3.9), a pooled NLR of 0.32 (95% CI: 0.25-0.40), a pooled DOR of 10 (95% CI: 7-15), and a pooled accuracy of 0.83 (95% CI: 0.79-0.86) for HCC detection (Table 2 and Figure 3).

With regards to the diagnostic ability of circRNAs as biomarkers in HCC detection, plasma sampling had higher sensitivity and specificity than other samples (pooled sensitivity=82% [95% CI: 71%-89%], pooled specificity=79% [95% CI: 62%-90%], Table 2). Besides, upregulated circRNAs (pooled sensitivity=77% [95% CI: 71%-83%], pooled specificity=78% [95% CI: 70%-85%], pooled DOR=12 [95% CI: 7-20]) had significantly higher sensitivity, specificity, and DOR than downregulated circRNAs (pooled sensitivity=73% [95% CI: 64%-81%], pooled specificity=73% [95% CI: 67%-78%], pooled DOR=7 [95% CI: 4-14], Table 2). Moreover, circRNAs including hsa_circ_0001445, circ-ADD3, and circ-0051443 were downregulated, while circRNAs including Has_circ_0004277, hsa_circ_0005397, and circ-LRIG3 (hsa_circ_0027345) were upregulated.

Diagnostic accuracy of circRNAs for Esophageal carcinoma

Eleven circRNAs as diagnostic biomarkers in esophageal carcinoma were extracted from eleven different articles, which involved various sample sources (Appendix Table A3). The highest sensitivity was related to Rong, June/ 2018, which was 67% (28), and the lowest sensitivity was related to Huang, E / 2020, which was 45% (29). The highest specificity was related to Li, X / 2020, which was 100% (30), and the lowest specificity was related to Hun, X.T / 2019, which was 22% (31). The overall and subgroup diagnostic ability of circRNAs for EC detection based on the expression of circRNAs and sample sources is shown in Table 2.

CircRNAs had an overall pooled sensitivity of 78% (95% CI: 74%-81%), a pooled specificity of 81% (95% CI: 69%-

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Table 2. The pooled estimates of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio of circRNAs in the detection of various gastrointestinal cancers

Cancer	Variable	Subgroups	Pooled Sensitivity (% 95 CI)	Pooled Specificity (% 95 CI)	Positive Likelihood Ratio (% 95 CI)	Negative Likelihood Ratio (% 95 CI)	Diagnostic Odds Ratio (DOR) (% 95 CI)	*P* value[#]
CRC	Overall	-	69 % (62 – 75 %)	57 % (49 – 66 %)	1.6 (1.3 – 2)	0.54 (0.42 – 0.70)	3 (2 – 5)	
	Expression Level	Downregulation	63 % (53 – 72 %)	57 % (45 – 67 %)	1.5 (1.1 – 1.9)	0.65 (0.48 – 0.90)	2 (1 – 4)	0.002
		Upregulation	73 % (66 – 80 %)	58 % (48 – 70 %)	1.7 (1.3 – 2.4)	0.46 (0.32 – 0.65)	4 (2 – 7)	
	Specimen Source	Plasma	76 % (67 – 83 %)	63 % (47 – 77 %)	2 (1.4 – 3)	0.39 (0.29 – 0.51)	5 (3 – 9)	0.033
		Serum	77 % (59 – 89 %)	64 % (51 – 75 %)	2.1 (1.4 – 3.4)	0.35 (0.17 – 0.75)	6 (2 – 19)	
		Tissue	61 % (52 – 69 %)	46 % (36 – 57 %)	1.1 (0.9 – 1.4)	0.85 (0.65 – 1.11)	1 (1 – 2)	
		Tissue & Plasma	80 % (68 – 88 %)	71 % (49 – 86 %)	2.7 (1.6 – 4.7)	0.29 (0.22 – 0.38)	9 (6 – 16)	
ES	Overall	-	78 % (74 – 81 %)	81 % (69 – 89 %)	4 (2.4 – 6.6)	0.28 (0.23 – 0.33)	15 (8 – 27)	
	Expression Level	Downregulation	79 % (67 – 88 %)	84 % (62 – 95 %)	5 (1.9 – 13)	0.25 (0.15 – 0.39)	20 (7 – 64)	0.088
		Upregulation	77 % (74 – 80 %)	77 % (63 – 87 %)	3.4 (2 – 5.7)	0.30 (0.25 – 0.35)	11 (6 – 22)	
	Specimen Source	Plasma	78 % (68 – 86 %)	85 % (70 – 93 %)	5.2 (2.6 – 10.5)	0.26 (0.18 – 0.38)	20 (9 – 45)	0.177
		Serum	-	-	-	-	-	
		Tissue	78 % (71 – 83 %)	80 % (55 – 93 %)	3.9 (1.4 – 10.5)	0.28 (0.18 – 0.43)	14 (3 – 56)	
		Tissue & Plasma	77 % (70 – 83 %)	71 % (43 – 89 %)	2.7 (1.2 – 6.0)	0.32 (0.25 – 0.40)	9 (3 – 22)	
GC	Overall	-	71 % (67 – 75 %)	75 % (71 – 79 %)	2.9 (2.4 – 3.5)	0.39 (0.33 – 0.45)	7 (5 – 10)	
	Expression Level	Downregulation	71 % (65 – 76 %)	75 % (68 – 81 %)	2.8 (2.1 – 3.8)	0.39 (0.32 – 0.48)	7 (5 – 11)	0.503
		Upregulation	71 % (66 – 76 %)	75 % (71 – 79 %)	2.9 (2.3 – 3.5)	0.39 (0.32 – 0.47)	7 (5 – 11)	
	Specimen Source	Plasma	69 % (53 – 82 %)	83 % (68 – 91 %)	4 (2.4 – 6.8)	0.37 (0.25 – 0.55)	11 (6 – 18)	0.439
		Serum	-	-	-	-	-	
		Tissue	68 % (63 – 73 %)	73 % (68 – 78 %)	2.5 (2.1 – 3.1)	0.43 (0.37 – 0.51)	6 (4 – 8)	
		Tissue & Plasma	74 % (68 – 80 %)	71 % (54 – 83 %)	2.5 (1.5 – 4.4)	0.36 (0.25 – 0.54)	7 (3 – 18)	
		Tissue & PBS	85 % (63 – 95 %)	88 % (69 – 96 %)	7.2 (2.1 – 24.9)	0.17 (0.05 – 0.54)	23 (4 – 44)	
HCC	Overall	-	76 % (70 – 81 %)	76 % (71 – 80 %)	3.2 (2.6 – 3.9)	0.32 (0.25 – 0.40)	10 (7 – 15)	
	Expression Level	Downregulation	73 % (64 – 81 %)	73 % (67 – 78 %)	2.7 (2 – 3.6)	0.37 (0.26 – 0.53)	7 (4 – 14)	0.004
		Upregulation	77 % (71 – 83 %)	78 % (70 – 85 %)	3.6 (2.6 – 4.9)	0.29 (0.22 – 0.38)	12 (7 – 20)	
	Specimen Source	Plasma	82 % (71 – 89 %)	79 % (62 – 90 %)	3.9 (2.1 – 7.2)	0.23 (0.15 – 0.35)	17 (9 – 33)	0.001
		Serum	74 % (67 – 80 %)	76 % (68 – 83 %)	3.1 (2.3 – 4.2)	0.34 (0.27 – 0.43)	9 (6 – 14)	
		Tissue	76 % (68 – 82 %)	76 % (70 – 81 %)	3.1 (2.4 – 4.1)	0.32 (0.24 – 0.43)	10 (6 – 17)	
		Blood	74 % (57 – 86 %)	70 % (64 – 75 %)	2.5 (1.9 – 3.3)	0.37 (0.20 – 0.67)	7 (3 – 16)	
PC	Overall	-	80 % (66 – 90 %)	75 % (69 – 80 %)	3.3 (2.4 – 4.4)	0.26 (0.14 – 0.49)	13 (5 – 31)	

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89%), and a pooled PLR of 4 (95% CI: 2.4-6.6), a pooled NLR of 0.28 (95% CI: 0.23-0.33), a pooled DOR of 15 (95% CI: 8-27), and a pooled accuracy of 0.81 (95% CI: 0.78-0.85) for EC detection (Table 2 and Figure 4). Eleven circRNAs were extracted from three sources of tissue, serum, and plasma in esophageal carcinoma, of which six were performed on plasma samples. Also, plasma samples had shown higher pooled sensitivity and pooled specificity than other samples (pooled sensitivity=78% [95% CI: 68%-86%], pooled specificity=85% [95% CI: 70%-93%], Table 2). The circRNAs that were recognized in EC were Circ-SLC7A5, hsa circ 0004771, hsa_circ_0006948, circRNA_141539, Circ0120816, circGSK3β, hsa_circ_0043603, has_circ_0026611, circ-DLG1, hsa_circRNA6448-14 and circ-TTC17. Almost all of circRNAs were up-regulated in EC whereas the expression level of hsa_circ_0043603 was decreased in EC. The most

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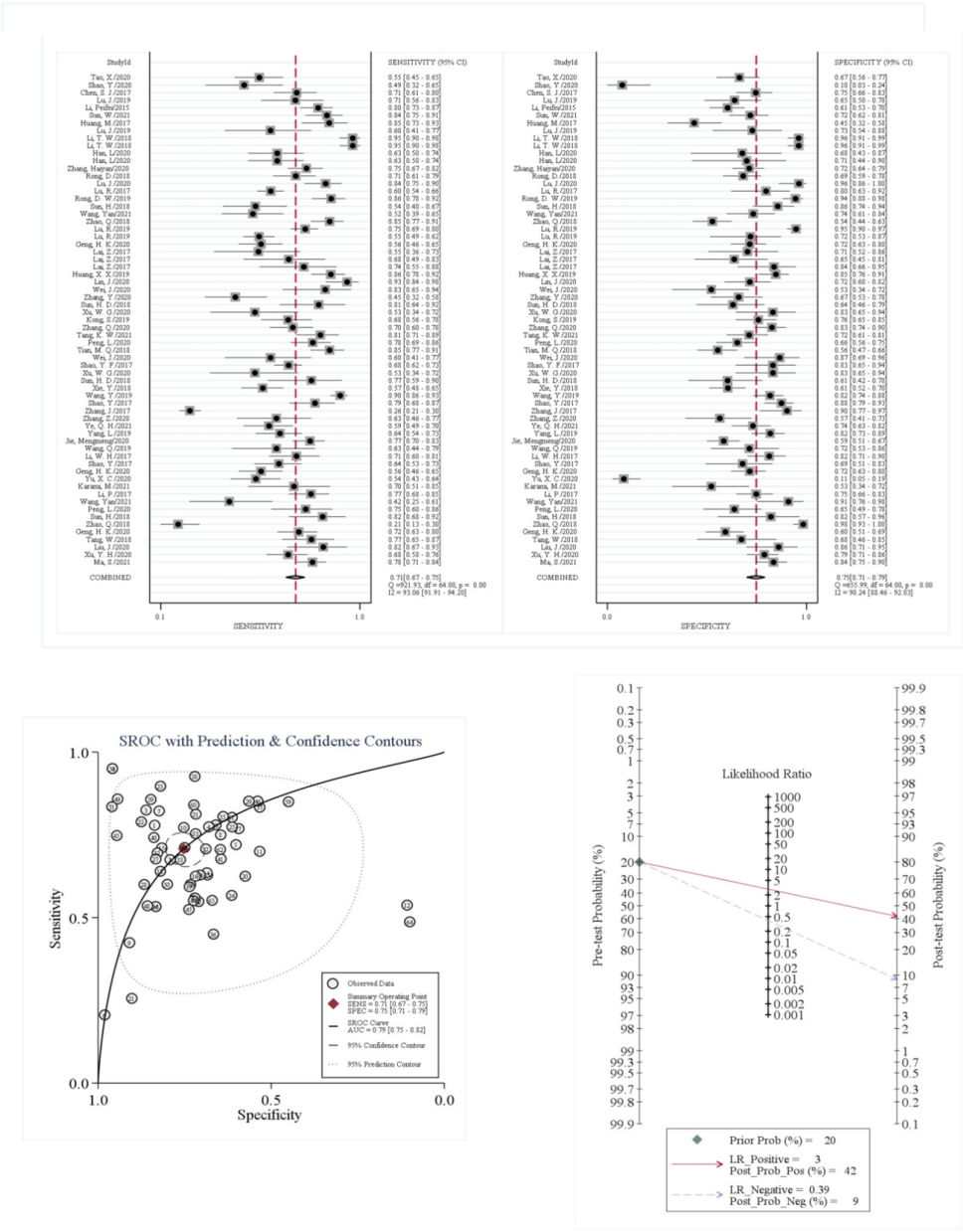

Figure 2. Meta-analysis plots of the diagnostic accuracy of circRNA to detect gastric cancer; a) pooled sensitivity and pooled specificity, b) Hierarchical summary receiver operating characteristic (HSROC) curve, c) the post-test probability of circRNAs.

important circRNAs as biomarkers of esophageal carcinoma included circ-SLC7A5, hsa_circ_0043603, circ-DLG1, circ-TTC17, all of which were up-regulated.

Diagnostic accuracy of circRNAs for colorectal cancer

Twenty-eight included studies introduced 30 circRNAs as biomarkers in the detection of CRC (Appendix Table A4). The highest sensitivity was related to Tian, J/ 2019, which was 0.95 (32), and the lowest sensitivity was related to Yang, N / 2020, which was 0.35 (33). The highest Specificity was related to Tian, J/ 2019 and Ye, D, X/2019, which was 0.87 (32, 34), and the lowest Specificity was related to Yang, N / 2020, which was 0.11 (33). CircRNAs had an overall pooled sensitivity of 69% (95% CI: 62%-75%), a pooled specificity of 57% (95% CI: 49%-66%), and a pooled PLR of 1.6 (95% CI: 1.3-2), a pooled NLR of 0.54 (95% CI: 0.42-0.70), pooled DOR of 3 (95% CI: 2-5), and a pooled accuracy of 0.68 (95% CI: 0.64-0.72) for CRC detection (Table 2 and Figure 5).

Studies on downregulated circRNAs had significantly higher sensitivity, specificity, and DOR than studies on up-regulated circRNAs. Two circRNAs, consisting of cir-

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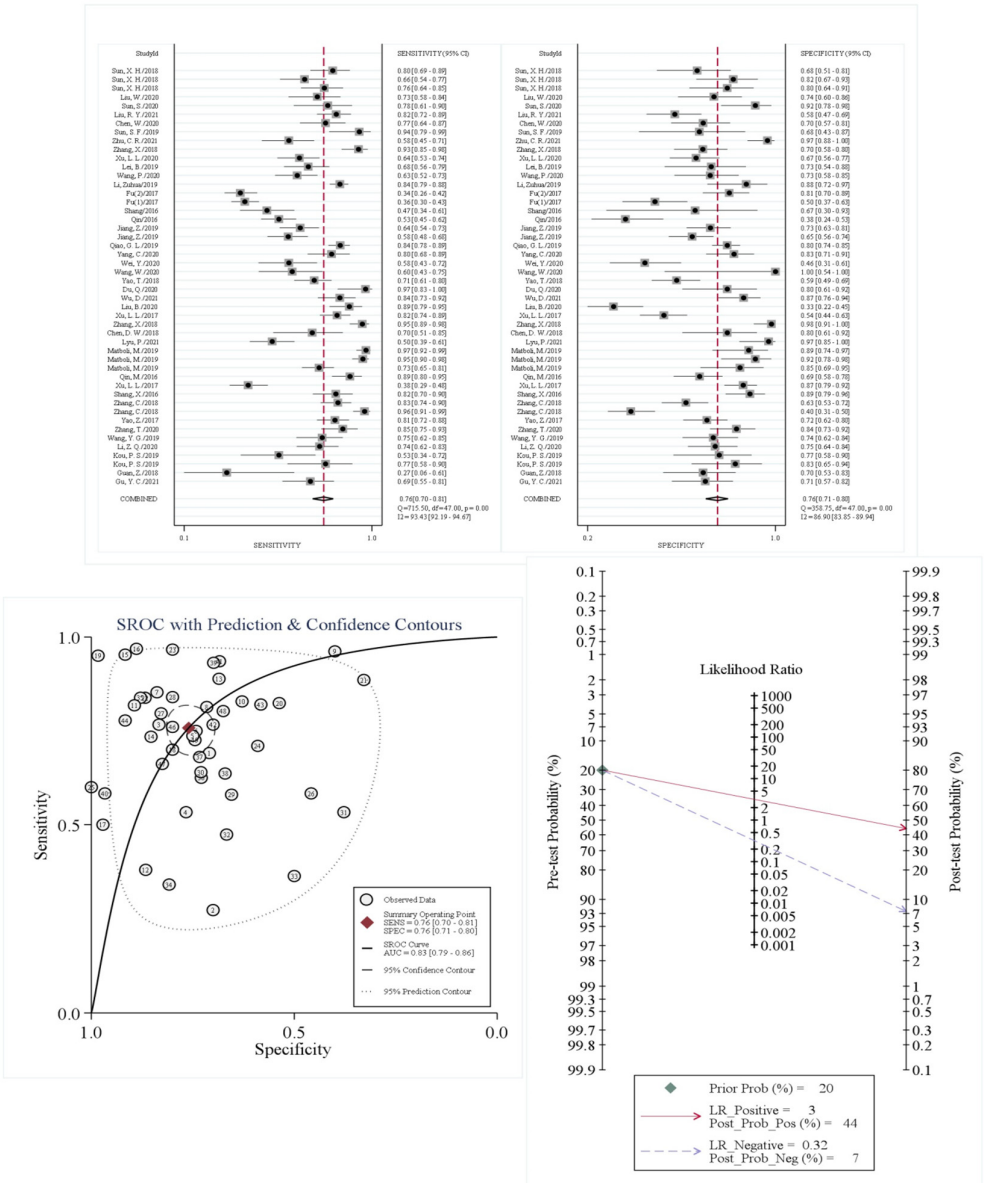

Figure 3. Meta-analysis plots of the diagnostic accuracy of circRNA to detect hepatocellular carcinoma; a) pooled sensitivity and pooled specificity, b) Hierarchical summary receiver operating characteristic (HSROC) curve, c) the post-test probability of circRNAs.

cZNF609, circMBOAT2, and hsa_circ_0002320 were important for CRC early detection, which were upregulated and downregulated, respectively.

Diagnostic accuracy of circRNAs for Pancreatic Cancer

Five circRNAs among five studies were listed for PC and accomplished on tissue and plasma samples (Appendix Table A5), and all of them showed upregulation. CircRNAs had an overall pooled sensitivity of 80% (95% CI: 66%-90%), a pooled specificity of 75% (95% CI: 69%-80%), and a pooled PLR of 3.3 (95% CI: 2.4-4.4), a pooled NLR of 0.26 (95% CI: 0.14-0.49), a pooled DOR of 13 (95% CI: 5-31), and a pooled accuracy of 0.78 (95% CI: 0.74-0.81) for PC detection (Table 2 and Figure 6). Besides, circLDLRAD3, hsa_circ_0000069, circEIF6, hsa_circ_0071036, and circ_001569 were obtained as the best biomarkers for PC early detection as they all became upregulated.

Discussion

GI tract malignancies remain a major global health burden, with rising incidence linked to dietary and lifestyle changes (35, 36). The early detection of GI cancers is crucial for improving treatment outcomes and survival. Biomarkers with stability, abundance, and tissue specificity are especially attractive, and circRNAs meet these requirements (37, 38). Beyond diagnostic potential, circRNAs

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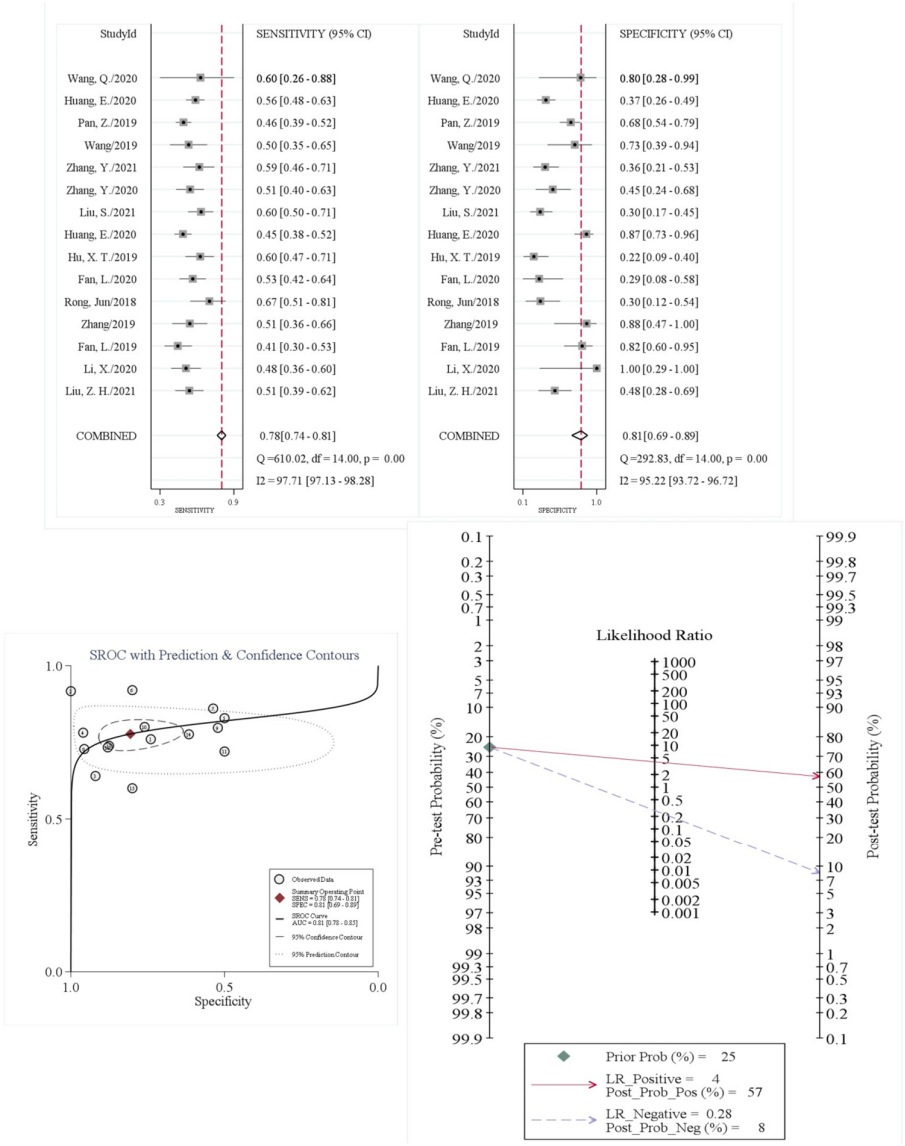

Figure 4. Meta-analysis plots of the diagnostic accuracy of circRNA to detect esophageal cancer; a) pooled sensitivity and pooled specificity, b) Hierarchical summary receiver operating characteristic (HSROC) curve, c) the post-test probability of circRNAs.

have been implicated in cell proliferation, metastasis, cancer stemness, and therapy resistance (39). Mechanistically, they influence tumor progression through pathways such as Wnt/β-catenin, MAPK/ERK, and PTEN/PI3K/AKT (40-42). This meta-analysis provides a comprehensive assessment of circRNAs as diagnostic biomarkers. We found good accuracy for HCC (AUC 0.83) and EC (AUC 0.81), moderate-to-good accuracy for GC (AUC 0.79) and PC (AUC 0.78), and limited accuracy for CRC (AUC 0.68). These findings suggest that circRNAs may be particularly valuable for HCC and EC detection, while their role in CRC remains restricted by lower specificity and higher false-positive rates. Importantly, heterogeneity across studies was substantial but could be partly explained by sample type and expression patterns. Plasma-based circRNAs consistently showed higher diagnostic accuracy than tissue-based assays (e.g., HCC: plasma sensitivity 82% vs. tissue 76%). Similarly, upregulated circRNAs demonstrated stronger diagnostic odds ratios than downregulated ones (12 vs. 7). These factors represent key sources of variability in published results. Specific circRNAs emerged as particularly promising biomarkers. For instance, hsa_circ_0001017 (GC), hsa_circ_0001445 (HCC), and circ-SLC7A5 (EC) showed strong performance, especially in plasma samples. Such circRNAs warrant further validation as non-invasive diagnostic tools. Nevertheless, the pooled accuracy metrics (generally below 80% sensitivity and specificity) indicate that circRNAs are not yet suitable as stand-alone diagnostic tests. Their greatest utility may lie

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in combination with established approaches such as imaging, biopsy, or conventional serum markers (e.g., AFP for HCC). Although circRNAs showed encouraging diagnostic accuracy, it is important to recognize that their performance remains insufficient for routine clinical use as stand-alone diagnostic tests. In diagnostic accuracy studies, sensitivity and specificity values approaching or exceeding 90% are typically required for reliable early detection. A major finding of this study is the presence of substantial heterogeneity across included analyses. This is not unexpected in biomarker meta-analyses, where differences in patient populations, study designs, and laboratory protocols often contribute to variability. Our subgroup and meta-regression analyses identified several contributors. First, specimen type had a significant impact: plasma-based circRNAs consistently outperformed tissue-based assays, especially in HCC (sensitivity 82% vs. 76%; specificity 79% vs. 76%). Second, expression direction was important, with upregulated circRNAs yielding higher diagnostic odds ratios (12) compared to downregulated circRNAs (7).

Third, regional bias may also have played a role, as most included studies originated from Asian cohorts, limiting generalizability. Together, these findings underscore the need for assay standardization and broader validation to minimize heterogeneity in future circRNA research. In our analysis, pooled sensitivity and specificity for most cancers were in the range of 70–80%, with CRC performing even lower. This indicates that circRNAs should be viewed as promising adjunct biomarkers, rather than definitive diagnostic tools. Their most practical application may be in combination with gold-standard methods such as imaging, biopsy, or established serum markers (e.g., AFP for HCC). This study has several limitations. Most included studies were from Asian populations, limiting generalizability.

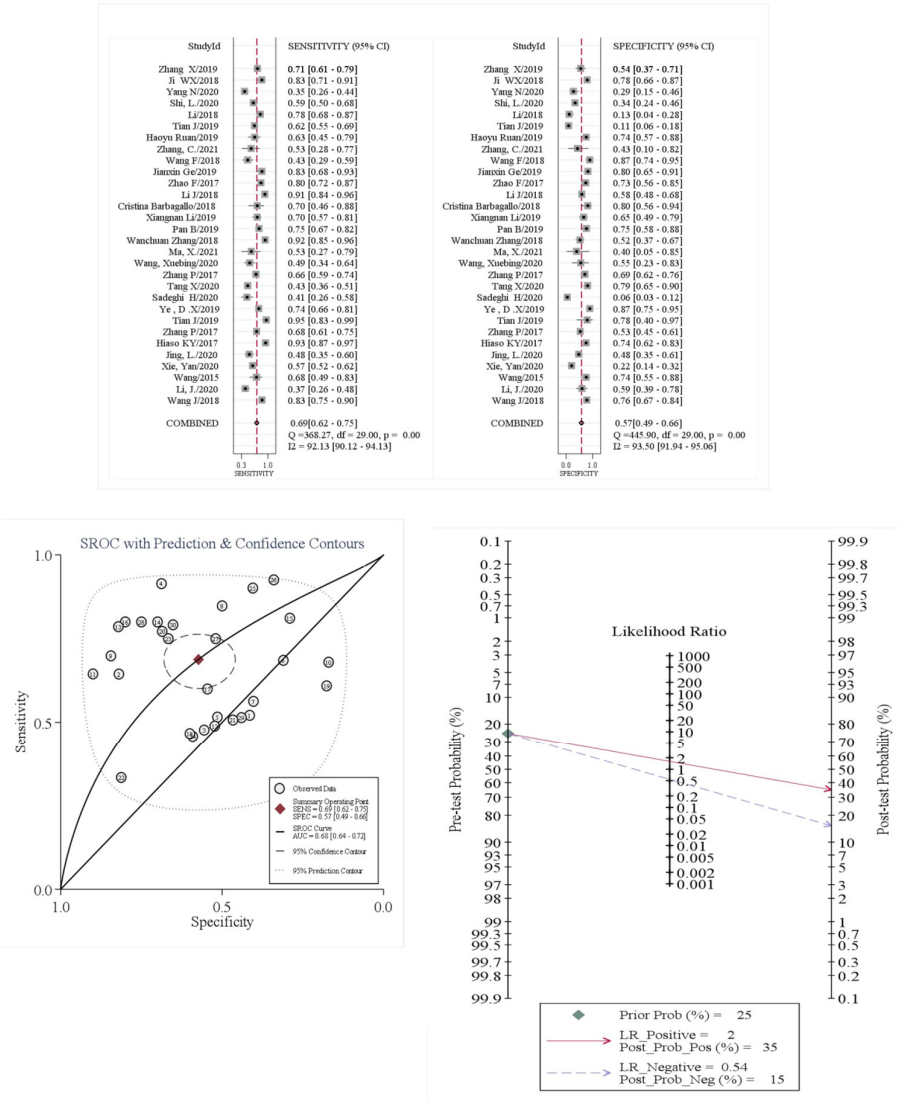

Figure 5. Meta-analysis plots of the diagnostic accuracy of circRNA to detect colorectal cancer; a) pooled sensitivity and pooled specificity, b) Hierarchical summary receiver operating characteristic (HSROC) curve, c) the post-test probability of circRNAs.

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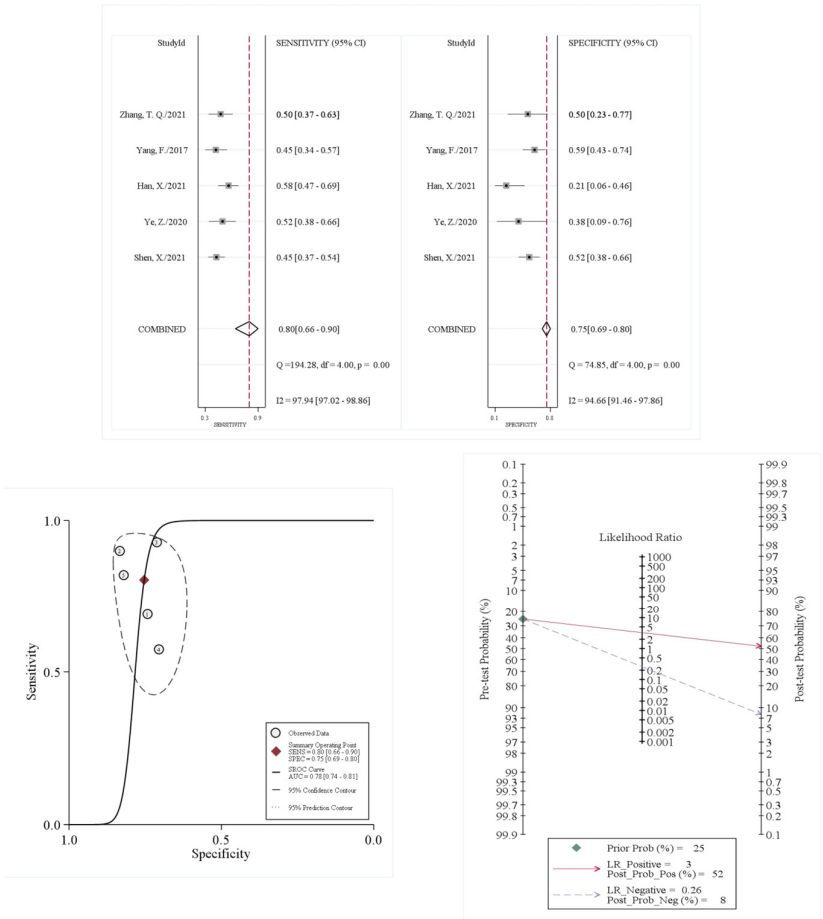

Figure 6. Meta-analysis plots of the diagnostic accuracy of circRNA to diagnose pancreatic cancer; a) pooled sensitivity and pooled specificity, b) Hierarchical summary receiver operating characteristic (HSROC) curve, c) the post-test probability of circRNAs.

Considerable heterogeneity was present, partly due to differences in specimen type, expression direction, and detection methods. The small number of studies in some cancers (PC and EC) reduced statistical power, and potential publication bias cannot be excluded. Finally, as with all meta-analyses, our findings depend on the quality of the original studies. Future studies should also explore the integration of circRNAs with established biomarkers in multi-marker panels to enhance diagnostic accuracy.

Conclusion

This updated meta-analysis assessed 153 circular RNAs (circRNAs) across 139 studies for their diagnostic performance in gastrointestinal cancers. CircRNAs showed good accuracy for hepatocellular carcinoma (AUC 0.83) and esophageal cancer (AUC 0.81), moderate accuracy for gastric (AUC 0.79) and pancreatic cancer (AUC 0.78), and limited accuracy for colorectal cancer (AUC 0.68). Plasma-based assays generally outperformed tissue-based ones, and upregulated circRNAs demonstrated stronger diagnostic value than downregulated ones, identifying these factors as key sources of heterogeneity. CircRNAs represent emerging non-invasive biomarkers with encouraging but moderate diagnostic accuracy. They show the greatest promise in HCC and EC but remain below clinical thresholds for independent diagnostic use. At present, circRNAs should be considered complementary tools alongside established diagnostic methods, and large multicenter validation studies are required to confirm their clinical utility."

Authors' Contributions

Conceptualization, SHN, ZB, YM; data curation, ZB, YM, GM, SHN; Formal analysis, YM; funding acquisition, not applicable; methodology, YM, HDB, GM, ZB, SN; project administration, SHN, YM; visualization, YM, ZB, SHN; writing—original draft, SHN, YM, ZB, HRD, BN, KHA, MA, HD; writing—review and editing, SHN, YM, ZB, BN, KHA, MA, MBK, ZV, HD. All authors have read and agreed to the published version of the manuscript.

Ethical Considerations

Not applicable.

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Dr. Yousef Moradi served as co–first author and contributed as the methodological expert in the design, analysis, and interpretation of this manuscript.

Conflict of Interests

The authors declare that they have no competing interests.

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Appendix Table A1. Characteristics of included studies for gastric cancer included in the meta-analysis.

Authors	Year	circRNA	Expression level	Specimen source	AUC	TP	FP	TN	FN	No. of patients	No. of controls	Sample size
Li, P.	2017	Circular RNA 0000096	Downregulation	Tissue	0.82	78	25	76	23	101	101	202
Karami, M.	2021	hsa-circ-0001724	Downregulation	Tissue	0.701	21	14	16	9	30	30	60
Yu, X. C.	2020	hsa_circ_0067582	Downregulation	Tissue	0.6937	50	83	10	43	93	93	186
Geng, H. K.	2020	circ_0005556	Upregulation	Tissue	0.635	66	33	85	52	118	118	236
Shao, Y.	2017	hsa_circ_0000705	Downregulation	Tissue	0.719	61	11	24	35	96	35	131
Han, L	2020	Hsa_circ_0021087	Downregulation	Tissue and PBS	0.7056	44	5	12	26	70	19	89
Han, L	2020	hsa_circ_0005051	Downregulation	Tissue and PBS	0.73	44	6	13	26	70	19	89
Li, W. H.	2017	hsa circ 0001649	Downregulation	Tissue	0.834	54	14	62	22	76	76	152
Lu, J.	2019	hsa_circ_0006848	Downregulation	Tissue and plasma	0.692	18	8	22	12	30	30	60
Huang, M.	2017	hsa_circ_0000745	Downregulation	Tissue and plasma	0.683	51	33	27	9	60	60	120
Sun, W.	2021	hsa_circ_0035445	Upregulation	Tissue and plasma	0.88	79	26	68	15	94	94	188
Li, Peifei	2015	Hsa_circ_002059	Downregulation	Tissue and plasma	0.73	110	53	84	27	137	137	374
Lu, J.	2019	Hsa_circ_0000467	Upregulation	Tissue and plasma	0.790	36	18	33	15	51	51	102
Chen, S. J.	2017	hsa_circ_0000190	Downregulation	Tissue and plasma	0.775	74	26	78	30	104	104	208
Wang, Q.	2019	Circ-EIF4G3	Upregulation	Tissue	0.7158	20	9	23	12	32	32	64
Peng, L.	2020	circCUL2	Downregulation	Serum	0.79	36	17	31	12	48	48	96
Jie, Meng-meng	2020	CircMRPS35	Downregulation	Tissue	0.6976	123	65	95	37	160	160	320
Yang, L.	2019	hsa_circ_0005556	Downregulation	Tissue	0.773	64	18	82	36	100	100	200
Ye, Q. H.	2021	hsa_circ_0001874	Downregulation	Tissue	0.673	54	24	67	37	91	91	182
Zhang, Z.	2020	CircDUSP16	Upregulation	Tissue	0.61	25	17	23	15	40	40	80
Zhang, J.	2017	circLARP4	Downregulation	Tissue	0.52	99	4	37	288	387	41	428
Shao, Y.	2017	Hsa_circ_0014717	Downregulation	Tissue	0.696	60	12	84	16	96	96	192
Wang, Y.	2019	hsa_circ_0005654	Downregulation	Tissue	0.924	270	22	100	31	301	122	423
Xie, Y.	2018	hsa circ 0074362	Downregulation	Tissue	0.630	72	49	78	55	127	127	254
Sun, H. D.	2018	circPVRL3	Downregulation	Tissue	0.7626	24	12	19	7	31	31	62
Ma, S.	2021	circPTPN22	Upregulation	Plasma	0.857	148	17	87	42	190	104	294
Xu, W. G.	2020	hsa-circ-0007766	Upregulation	Tissue	0.704	16	5	25	14	30	30	60
Shao, Y. F.	2017	hsa_circ_0001895	Downregulation	Tissue	0.792	174	5	25	83	257	30	287
Wei, J.	2020	hsa_circRNA_102958	Upregulation	Tissue	0.74	18	4	26	12	30	30	60
Tian, M. Q.	2018	hsa_circ_0003159	Downregulation	Tissue	0.75	92	47	61	16	108	108	216
Xu, Y. H.	2020	Circ_0004771	Upregulation	Plasma	0.831	81	25	95	39	120	120	240
Peng, L.	2020	circCUL2	Downregulation	Tissue	0.790	78	34	66	22	100	100	200
Tang, K. W.	2021	Circ_0049447	Downregulation	Tissue	0.838	65	24	61	15	80	80	160
Zhang, Q.	2020	circCCDC66	Upregulation	Tissue	81.5%	73	18	87	32	105	105	210
Kong, S.	2019	hsa_circ_0001821	Downregulation	Tissue	0.792	54	19	61	26	80	80	160
Rong, D. W.	2019	CircPSMC3	Downregulation	Tissue and plasma	0.9326	91	6	100	15	106	106	212
Lu, R.	2017	hsa_circ_0006633	Downregulation	Tissue and plasma	0.741	182	7	28	121	303	35	338
Lu, J.	2020	circ-RanGAP1	Upregulation	Tissue and plasma	0.646	81	2	48	16	97	97	194
Liu, J.	2020	circ-MAT2B	Upregulation	Plasma	0.8875	33	5	31	7	40	36	76
Tang, W.	2018	circ-KIAA1244	Downregulation	Plasma	0.7481	48	8	17	14	62	25	77
Rong, D.	2018	circ_0066444	Upregulation	Tissue and plasma	0.7328	75	33	73	31	106	106	212
Xu, W. G.	2020	hsa-circ-0007766	Upregulation	Tissue	0.704	16	5	25	14	30	30	60
Tao, X.	2020	circ 0000419	Downregulation	Tissues	0.642	53	28	57	43	96	85	181
Sun, H. D.	2018	Circ-sFMBT2	Upregulation	Tissue	0.7585	29	13	23	7	36	36	72
Zhang, Hai-yan	2020	hsa_circ_0001811	Downregulation	Tissue and plasma	0.824	107	40	102	35	142	142	284
Zhang, Y.	2020	Hsa_circ_0023642	Upregulation	Tissue	0.6422	27	20	40	33	60	60	120

Abbreviations: circRNA, circular RNA; AUC, area under the curve; TP, true positive; FP, false positive; FN, false negative; TN, true negative

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Appendix Table A1. Characteristics of included studies for gastric cancer included in the meta-analysis.

Authors	Year	circRNA	Expression level	Specimen source	AUC	TP	FP	TN	FN	No. of patients	No. of controls	Sample size
Wei, J.	2020	circHIPK3	Upregulation	Tissue	0.743	25	14	16	5	30	30	60
Lin, J.	2020	circCYFIP2	Upregulation	Tissue	0.947	63	19	49	5	68	68	136
Huang, X. X.	2019	hsa_circ_0000199	Upregulation	Tissue	0.91	90	16	89	15	105	105	210
Lai, Z.	2017	hsa_circ_0047905	Upregulation	Tissue	0.85	23	5	26	8	31	31	62
Lai, Z.	2017	hsa_circ_0138960	Upregulation	Tissue	0.647	21	11	20	10	31	31	62
Lai, Z.	2017	hascircRNA7690-15	Upregulation	Tissue	0.681	17	9	22	14	31	31	62
Geng, H. K.	2020	hsa_circ_0005556	Upregulation	Tissue	0.635	66	33	85	52	118	118	236
Geng, H. K.	2020	hsa_circ_0005556	Upregulation	Plasma	0.635	85	47	71	33	118	118	236
Lu, R.	2019	circ_0067582	Downregulation	Tissue	0.671	129	8	21	105	234	29	263
Lu, R.	2019	hsa_circ_0005758	Downregulation	Tissue	0.721	175	10	175	59	234	29	263
Zhao, Q.	2018	hsa_circ_0000181	Downregulation	Tissue	0.756	98	53	62	17	115	115	230
Zhao, Q.	2018	hsa_circ_0000181	Downregulation	Plasma	0.582	21	2	103	81	102	105	207
Li, T. W.	2018	hsa_circ_0001017	Downregulation	Tissue and PBS	0.966	115	5	116	6	121	121	242
Li, T. W.	2018	hsa_circ_0061276	Downregulation	Tissue and PBS	0.966	115	5	116	6	121	121	242
Shao, Y.	2020	circ_0065149	Downregulation	Tissue and plasma and gastric juice	0.640	19	36	4	20	39	41	80
Wang, Yan	2021	Circular RNA ITCH	Downregulation	Tissue	0.7055	32	16	45	29	61	61	122
Wang, Yan	2021	Circular RNA ITCH	Downregulation	Serum	0.6535	14	3	30	19	33	33	66
Sun, H.	2018	hsa_circ_0000520	Downregulation	Tissue	0.6129	30	8	48	26	56	56	112
Sun, H.	2018	hsa_circ_0000520	Downregulation	Plasma	0.8967	37	3	14	8	45	17	62

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Appendix Table A2. Characteristics of included studies for hepatocellular carcinoma included in the meta-analysis.

Author	Year	circRNA	Expression level	Specimen source	AUC	TP	FP	TN	FN	No. of patients	No. of contr
Zhang, X.	2018	hsa_circ_0001445	Downregulation	Plasma	0/862	68	22	51	5	73	73
Li, Zuhua	2019	circSMARCA5	Downregulation	Tissue and plasma	0/938	223	4	29	43	266	33
Gu, Y. C.	2021	hsa_circ_0123629	Upregulation	Tissue	0/7369	38	16	39	17	55	55
Guan, Z.	2018	hsa_circ_0016788	Upregulation	Tissue	0/851	3	12	28	8	40	40
Kou, P. S.	2019	hsa_circ_0078602	Downregulation	Tissue	0/787	23	5	25	7	30	30
Kou, P. S.	2019	hsa_circ_0018764	Downregulation	Tissue	0/676	16	7	23	14	30	30
Li, Z. Q.	2020	hsa_circ_0056836	Downregulation	Tissue	0/8742	56	19	57	20	76	76
Xu, L. L.	2020	circSETD3	Downregulation	Blood	0/637	56	29	59	32	88	88
Liu, W.	2020	circ_0091579	Upregulation	Serum	0/771	37	12	35	14	51	47
Zhu, C. R.	2021	Has- circ-0004277	Upregulation	Plasma	0/816	35	2	58	25	60	60
Wang, Y. G.	2019	hsa_circ_0091570	Downregulation	Tissue	0/736	45	16	46	15	60	60
Zhang, T.	2020	circTMEM45A	Upregulation	Tissue	0/888	58	11	57	10	68	68
Yao, Z.	2017	circZKSCAN1	Downregulation	Tissue	0/834	83	29	73	19	102	102
Zhang, C.	2018	Hsa_Circ_0091579	Upregulation	Tissue	0/656	101	63	42	4	105	105
Zhang, C.	2018	hsa_circ_16245-1	Upregulation	Tissue	0/72	87	39	66	18	105	105
Shang, X.	2016	hsa_circ_0005075	Upregulation	Tissue	0/94	54	7	59	12	66	66
Sun, X. H.	2018	hsa_circ_0004001	Upregulation	Serum	0/79	54	8	32	17	71	40
Sun, X. H.	2018	hsa_circ_0004123	Upregulation	Serum	0/73	47	7	33	24	71	40
Sun, X. H.	2018	hsa_circ_0075792	Upregulation	Serum	0/76	57	13	27	14	71	40
Qin, M.	2016	Hsa_circ_0001649	Downregulation	tissue	0/63	72	28	61	9	89	89
Matboli, M.	2019	hsa_circ_00156	Downregulation	tissue	0/839	94	5	29	34	128	36
Matboli, M.	2019	hsa_circ _000224	Downregulation	tissue	0/974	122	3	33	6	128	36
Matboli, M.	2019	hsa_circ_000520	Downregulation	tissue	0/943	124	4	32	4	128	36
Lyu, P.	2021	CircWHSC1	Upregulation	tissue	0/8692	42	1	34	42	50	35
Chen, D. W.	2018	hsa_circ_0128298	Upregulation	tissue	0/668	21	6	24	9	30	30
Zhang, X.	2018	circRNA_104075	Upregulation	tissue	0/973	96	1	59	5	101	60
Wang, P.	2020	circSETD3	Downregulation	Blood	0/637	55	13	35	33	88	48
Xu, L. L.	2017	ciRS-7	Upregulation	tissue	0/68	89	50	58	19	108	108
Sun, S. F.	2019	circ-ADD3	Downregulation	Plasma	0/8878	29	6	13	2	31	19
Liu, B.	2020	CircBACH1 (hsa_circ_0061395)	Upregulation	tissue	0/8506	62	47	23	8	70	70
Wu, D.	2021	circRASGRF2	Upregulation	tissue	0/882	57	9	59	11	68	68
Lei, B.	2019	circ_0000798	Upregulation	Blood	0/703	49	8	22	23	72	30
Chen, W.	2020	circ-0051443	Downregulation	Plasma	0/8089	46	18	42	14	60	60
Liu, R. Y.	2021	hsa_circ_0005397	Upregulation	Plasma	0/737	73	33	46	16	89	79
Du, Q.	2020	hsa_circ_0008450	Upregulation	tissue	0/97	29	6	24	1	30	30
Yao, T.	2018	Hsa_circ_0068669	Downregulation	tissue	0/64	71	41	59	29	100	100
Sun, S.	2020	circ-LRIG3 (hsa_circ_0027345)	Upregulation	Plasma	0/8681	28	3	33	8	36	36
Wang, W.	2020	circ-FOXP1	Upregulation	tissue	0/9318	24	0	6	16	30	16
Wei, Y.	2020	circ-CDYL	Upregulation	tissue	0/64	28	26	22	20	48	48
Yang, C.	2020	circFN1	Upregulation	tissue	0/878	51	11	53	13	64	64
Qiao, G. L.	2019	Hsa_circ_0003998	Upregulation	tissue	0/894	168	40	160	32	200	200
Jiang, Z.	2019	Hsa_circ_0028502	Downregulation	tissue	0/675	58	38	72	42	100	100
Jiang, Z.	2019	hsa_circ_0076251	Downregulation	tissue	0/738	64	27	73	36	100	100
Qin	2016	hsa-circ-0001649	Downregulation	Tissue	0/63	72	28	17	63	89	89
Shang	2016	hsa-circ-0005075	Upregulation	Tissue	0/94	27	3	6	30	33	33
Fu (1)	2017	hsa-circ-0004018	Downregulation	Tissue	0/848	73	29	29	128	102	157
Fu (2)	2017	hsa-circ-0003570	Downregulation	Tissue	0/7	48	14	59	93	107	107

Abbreviations: circRNA, circular RNA; AUC, area under the curve; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

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Appendix Table A3. Characteristics of included studies for esophageal carcinoma included in the meta-analysis

Author	Year	circRNA	Expression level	Specimen source	AUC	TP	FP	TN	FN	No. of patients	No. of controls	Sample si
Wang, Q.	2020	Circ-SLC7A5	Upregulated	Plasma	0/7717	6	1	4	4	10	5	15
Huang, E.	2020	hsa circ 0004771	Upregulated	Tissue and plasma	0/672	91	5	110	34	125	125	250
Pan, Z.	2019	hsa_circ_0006948	Upregulated	Tissue	0/85	113	19	134	40	153	153	306
Liu, Z. H.	2021	circRNA_141539	Upregulated	Tissue	0/8098	38	13	37	12	50	50	100
Li, X.	2020	Circ0120816	Upregulated	Tissue	--	33	0	36	3	36	36	72
Hu, X. T.	2019	circGSK3β	Upregulated	Tissue and plasma	0/782	43	25	29	7	50	50	100
Fan, L.	2019	hsa_circ_0043603	Downregulated	Plasma	0/836	32	4	46	18	50	50	100
Liu, S.	2021	has_circ_0026611	Upregulated	Serum	0/724	55	33	36	14	69	69	138
Rong, Jun	2018	circ-DLG1	Upregulated	Plasma	0/648	29	14	14	6	35	28	91
Zhang, Y.	2020	hsa_circRNA6448-14	Upregulated	Tissue	0/846	40	12	38	10	50	50	100
Wang	2019	circ-TTC17	Upregulated	Plasma	0/82	22	3	22	8	30	25	55

Abbreviations: circRNA, circular RNA; AUC, area under the curve; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

Appendix Table A4. Characteristics of included studies for colorectal cancer included in the meta-analysis.

Author	Year	circRNA	Expression level	Specimen source	AUC	TP	FP	TN	FN	No. of patients	No. of controls	Sample size
Wang J	2018	hsa-circ-0000567	D	Tissue	0/8653	85	24	17	78	102	102	204
Wang F	2018	hsa-circ-0014717	D	Tissue	0/683	20	6	26	40	46	46	92
Hiaso KY	2017	circCCDC66	Upregulated	Tissue	0/88	122	20	9	56	131	76	207
Zhang P	2017	hsa-circRNA-104700	D	Tissue	0/699	113	52	57	118	170	170	340
Zhang P	2017	hsa-circRNA103809	D	Tissue	0/616	116	80	54	90	170	170	340
Li J	2018	hsa-circ-0000711	D	Tissue	0/81	92	42	9	59	101	101	202
Ji WX	2018	hsa-circ-0001649	Upregulated	Tissue	0/857	53	14	11	50	64	64	128
Zhao F	2017	CircRNA0003906	D	Plasma	0/818	98	11	24	29	122	40	162
Cristina Barbagallo	2018	hsa-circ-0000284	Upregulated	Serum	0/771	14	4	6	16	20	20	40
Wanchuan Zhang	2018	hsa-circ-0007534	Upregulated	Plasma	0/78	103	22	9	24	112	46	158
Haoyu Ruan	2019	hsa-circ-0002138	D	Tissue	0/725	22	9	13	26	35	35	70
Jianxin Ge	2019	hsa-circ-0142527	D	Tissue	0/818	34	8	7	33	41	41	82
Li	2018	circITGA7	D	Tissue	0/879	62	33	17	5	69	48	117
Xiangnan Li	2019	hsa-circ-0006990	Upregulated	Plasma	0/724	42	15	18	28	60	43	103
Ma, X.	2021	circ_0115744	Upregulated	Plasma	0/79	8	3	7	2	10	10	20
Zhang, C.	2021	hsa_circ_0006401	D	Tissue	0/77	9	4	8	3	12	12	24
Shi, L.	2020	hsa_circ_0000826	Upregulated	Serum	0/7778	75	48	52	25	100	100	200
Jing, L.	2020	hsa_ circ_0044556	Upregulated	Tissue	0/7274	32	33	35	30	52	52	104
Wang, Xuebing	2020	circ_0060745	Upregulated	Tissue	0/8442	22	5	23	6	28	28	54
Xie, Yan	2020	circ-PNN (hsa_circ_0101802)	Upregulated	serum	0/854	202	69	152	19	221	221	442
Sadeghi H	2020	hsa_circ_0060927	Upregulated	Tissue	0/78	17	117	24	8	83	83	166
Tian J	2019	CircRNA hsa_circ_0004585	Upregulated	PBS	0/707	109	97	66	12	142	142	284
Yang N	2020	Hsa_circ_0002320	D	Tissue and Plasma	0/823	40	25	75	10	50	100	150
Ye, D .X	2019	Hsa_circ_0082182	Upregulated	Plasma	0/8346	109	7	38	47	156	45	201
Ye, D .X	2019	hsa_circ_0000370	Upregulated	Plasma	0/8346	109	7	38	47	156	45	201
Ye, D .X	2019	hsa_circ_0035445	Upregulated	Plasma	0/8346	109	7	38	47	156	45	201
Zhang X	2019	circZNF609	D	Tissue and serum	0/767	72	16	30	19	91	46	137
Pan B	2019	hsa-circ-0004771	Upregulated	serum	0/92	108	9	36	27	135	45	180
Tang X	2020	circMBOAT2	Upregulated	Tissues and serum	0/75	69	10	90	38	107	100	207
Wang	2015	hsa-circ-001988	D	Tissue	0/788	21	8	10	23	31	31	62

Abbreviations: circRNA, circular RNA; AUC, area under the curve; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

Appendix Table A5. Characteristics of the included studies for pancreatic cancer included in the meta-analysis.

Author	Year	circRNA	Expression level	Specimen source	AUC	TP	FP	TN	FN	No. of patients	NO. of controls	Sample size
Yang, F.	2017	circ-LDLRAD3	U	Tissue and plasma	0/67	35	18	43	26	61	61	122
Ye, Z.	2020	hsa_circ_0000069	U	Tissue	0/8944	27	5	25	3	30	30	60
Zhang, T. Q.	2021	circEIF6	U	Tissue	0/9093	32	7	32	7	39	39	78
Han, X.	2021	hsa_circ_0071036	U	Tissue	0/65	52	15	37	4	56	56	112
Shen, X.	2021	circ_001569	U	Plasma	0/716	60	25	72	27	97	97	194

Abbreviations: circRNA, circular RNA; AUC, area under the curve; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

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