MicroRNA-21 as a Potential Biomarker for Colorectal Cancer Diagnosis: A Meta-analysis

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Authors' contributions

This work was carried out in collaboration between all authors. Author CHZ wrote the protocol and the first draft of the manuscript. Author GJY collected, processed and analyzed data. Author YT managed the literature searches. Author LY designed research and contributed to interpretation of data. Authors XFY and FRL contributed to research design, revising the paper critically and approval of the submitted and final versions. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aims: Colorectal cancer (CRC) occupies an important position in the morbidity and mortality constitution of malignancies. In recent years, mounting literature has reported about the upregulating expression of microRNA-21 in blood and stool of CRC patients, which suggested that microRNA-21 may become a novel potential biomarker for CRC. Consequently, this meta-analysis was designed to systematically review the values of microRNA-21 in CRC diagnosis.

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Methodology: Databases, including Cochrane library, PubMed, EMbase, Google Scholar, and Chinese National Knowledge Infrastructure, were scanned to retrieve relevant articles focusing on microRNA-21 in CRC diagnosis. Articles were then filtered according to the PRISMA statement and assessed by quality assessment of diagnosis accuracy studies-2. Sensitivity (SEN), specificity (SPE), positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) were pooled using fixed-effects model or random-effects model. Summary receiver operating characteristic (SROC) curve and area under the curve (AUC) were used to estimate the overall diagnostic performance.
Results: A total of 15 studies, comprising 1268 CRC patients and 910 healthy controls, were enrolled in this meta-analysis. For serum miR-21, the pooled DOR, SEN, and SPE were 13.97 (95% CI: 8.44–23.11), 0.73 (95% CI: 0.69–0.77), and 0.83 (95% CI: 0.76–0.89), respectively; for plasma miR-21, the pooled DOR, SEN, and SPE were 8.03 (95% CI: 3.30–19.52), 0.67 (95% CI: 0.60–0.73), and 0.76 (95% CI: 0.69–0.81), respectively; and for fecal miR-21, the pooled DOR, SEN, and SPE were 7.06 (95% CI: 2.17–22.95), 0.33 (95% CI: 0.28–0.37), and 0.91 (95% CI: 0.88–0.93), respectively. Moreover, the AUC values of serum, plasma, and fecal miR-21 in CRC diagnosis were 0.8701, 0.8295, and 0.6742, respectively.
Conclusion: Blood miR-21 demonstrates good diagnostic performance, and serum samples are better than plasma samples in CRC diagnosis. For fecal miR-21, the sensitivity is unsatisfactory, but the specificity is favorable in predicting CRC patients.

1. INTRODUCTION

In recent years, morbidity and mortality constitution of tumors published worldwide has demonstrated that [1-3] colorectal cancer is increasingly threatening to human health. Although early detection, early diagnosis, and early treatment are emphasized in clinical practice, limitations still exist in the present imaging technology for early diagnosis of colorectal cancer (CRC) [4,5]. For example, nuclear magnetic resonance imaging, computed tomography, and positron emission computed tomography show limitations of high cost, selective sizes of tumor tissues, and disconfirmation; air barium double-contrast radiography examination, transrectal ultrasound, and colonoscopy are usually rejected because of discomfort during operation [6]. Furthermore, serum tumor markers [7] and fecal occult-blood testing (FOBT) [8] exhibit low sensitivity and unsatisfactory specificity.

MicroRNAs (miRNAs) are evolutionarily conserved, endogenous, and non-coding RNA molecules, which consist of 17–25 nucleotides and can identify specific target mRNAs to act as negative gene regulators at post-transcriptional level. Considerable research has found that abnormal miRNA expression emerges in the occurrence and development of CRC, and tumor-specific miRNA exists in CRC patients' serum, plasma [9,10], feces [11] or tissue [12,13]; all of which can be stably detected and can predict tumor status; such discoveries ensure a promising application prospect for miRNAs as novel tumor biomarkers.

As a widely studied oncogenic miRNA, miR-21 has been notably upregulated in CRC patients. Previous studies proposed that miR-21 is positively correlated with pathological staging of CRC and negatively correlated with disease-free interval [14,15]. Additionally, miR-21 is considered a powerful prognostic marker applicable to CRC patients from various racial populations, and it can identify the progression of high-risk diseases in the early stage of cancer [16,17]. This meta-analysis was conducted to evaluate the clinical values of miR-21 in tissues, feces, serum, and plasma for systematic diagnosis of CRC.

2. MATERIALS AND METHODS

2.1 Search Strategy

All relevant articles were searched via the following electronic databases: Cochrane library, PubMed, EMbase, Google Scholar, and Chinese National Knowledge Infrastructure until January 10, 2015. Brief search strategies were as follows: ("Subject headings" or colorectal cancer or colon cancer or rectal cancer), ("Subject headings" or microRNA-21 or miRNA-21), ("Subject headings" or sensitivity or specificity), and other precise search strategies of PubMed (Table 1).

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion criteria

(1) all CRC patients were pathologically verified (gold standard); (2) CRC patients did not receive radiotherapy, chemotherapy, surgery nor any other treatment before sample collection; (3) studies had to contain evaluating indicators of microRNA-21 used alone for CRC diagnosis: sensitivity or specificity; (4) normal controls were set; (5) for similar literature published by the same author or research center, those with more recent publication time or higher influence factor were included，and resemble studies focusing on different indicators should all be involved; (6) cases of each group should be ≥10; (7) no restriction in age, gender, nationality, and race, and original articles published in either English or Chinese.

2.2.2 Exclusion criteria

(1) duplicate publications; (2) missing data cannot be quantitatively synthesized; (3) non-human studies, cell researches, reviews, meta-analysis, meeting abstracts, or case reports.

2.3 Data Extraction and Quality Assessment

On the basis of the above mentioned inclusion and exclusion criteria, two investigators (Chaohui ZHEN and Guojun YAO) independently conducted literature selection, quality assessment, and data extraction. Any disagreement would be fully discussed between the former two researchers, or under the assistance of the third senior investigator to reach a consensus. The final enrolled articles were assessed by referring to quality assessment of diagnosis accuracy studies-2 (QUADAS-2) [18]. In diagnostic tests, QUADAS-2 was generally recognized as a quality assessing tool comprising four domains: (1) patient selection; (2) index test; (3) reference standard; and (4) flow and timing. The signaling questions of each domain are rated as "high," "unclear," and "low" to judge on risk of bias and applicability.

Table 1. Search strategy in PubMed

Search	Query	Items found
#26	Search (#15 and #21 and #25)	28
#25	Search (#22 or #23 or #24)	1420495
#24	Search specificity	968466
#23	Search sensitivity	956430
#22	Search "Sensitivity and Specificity""[Mesh]"	425515
#21	Search (#16 or #17 or #18 or #19 or #20)	1925
#20	Search microRNA-21	493
#19	Search hsa-mir-21	45
#18	Search miR-21	1744
#17	Search miRNA-21	132
#16	Search "MIRN21 microRNA, human"" [Supplementary Concept]"	678
#15	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)	218734
#14	Search Rectum Cancer	58167
#13	Search Rectal Tumor	52294
#12	Search Rectum Neoplasm	53031
#11	Search rectal cancer	54338
#10	Search "Rectal Neoplasms""[Mesh]"	38098
#9	Search Colonic Cancer	80002
#8	Search Colon Neoplasm	85757
#7	Search colon cancer	111006
#6	Search "Colonic Neoplasms""[Mesh]"	67680
#5	Search CRC	19972
#4	Search Colorectal Carcinoma	162235
#3	Search Colorectal Tumor	164676
#2	Search colorectal cancer	172563
#1	Search "Colorectal Neoplasms""[Mesh]"	150393

2.4 Statistical Analysis

All statistical analyses were performed by Meta-DiSc and STATA12.0 statistical software. By extracting all relevant data (true positives, false positives, true negatives, and false negatives) from the enrolled studies, the pooled sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and 95% confidence interval (95% CI) were obtained. Simultaneously, the investigators generated the summary receiver operating characteristic (SROC) curve and calculated the area under the curve (AUC). The analysis steps were as follows: (1) Heterogeneity test: a. The threshold effect was assessed using Spearman correlation coefficient [19]; a P value < 0.05 suggested the presence of the threshold effect requiring no meta-analysis; b. The non-threshold effect was detected by Cochran-Q method and test of inconsistency index ($I2$) [20]; a low P value of <0.05 or a high $I2$ value of >50% suggested the existence of non-threshold effect, and meta-regression analysis was consequently used to determine the sources; (2) Meta-regression analysis: The research-related covariates were compared, which were eliminated one-by-one based on the P values (from high to low); the covariates causing heterogeneity were determined, and subgroup analysis was performed; (3) Quantitative synthesis: a. Fixed-effects model (Mantel-Haenszel method) was used to combine the data if heterogeneity did not exist; b. Subgroup analysis or random-effects model (DerSimonian-Laird method) was applied to combine the data if non-threshold effect existed; (4) Publication bias was assessed by Begg's test and Egger's test [21]; a P value ≥ 0.05 indicated no publication bias.

3. RESULTS

3.1 Characteristics of Eligible Studies

After selection based on PRISMA statement [22], about 15 studies with a total of 1268 CRC patients and 910 healthy controls were eventually eligible. Fig. 1 shows the study selection process, and Table 2 lists the main characteristics of the eligible studies.

3.2 Quality Assessment

The quality of the included studies was assessed using QUADAS-2 quality assessment. All 15 inclusions reached middle to high quality (Figs. 2 and 3). However, no blinding method was set in the detection of gold standard. Hence, a major bias was concentrated upon "index test"; bias also existed in "patient selection" because most of the research did not report nor recruit patients randomly.

3.3 Heterogeneity Test

The heterogeneity among the studies is a critical factor influencing the accuracy of the synthesis. We first evaluated the existence of the threshold effect by calculating the Spearman correlation coefficient and P values (less than three studies about tissue samples were included; thus, heterogeneity test was not performed). The results showed that the SROC curves of blood (serum and plasma), serum, plasma, and fecal samples were not shoulder-shaped. For blood samples, the Spearman correlation coefficient and P value were −0.117 and 0.765, whereas 0.400 and 0.600 for serum samples, respectively; for plasma samples and fecal samples, the corresponding values were −0.500 and 0.391; and 0.500 and 0.667, respectively; all of which indicated that the threshold effect did not exist. Moreover, the P value of Cochran-Q method and the I^2 value were employed to detect the existence of the non-threshold effect. The pooled SEN, SPE, PLR, NLR, and DOR of blood, plasma, and fecal samples obtained a P value of <0.05 and an I^2 value of >50%, thus indicating that heterogeneity caused by non-threshold effect exists in these samples, and meta-regression analysis should be performed. For serum samples, the pooled SPE, PLR, and DOR showed a P value of >0.05 and an I^2 value of <50%, which can be directly merged by FEM; the pooled SEN and NLR indicated a P value of <0.05 and an I^2 value of >50%. Thus, meta-regression was applied.

3.4 Meta-regression

Meta-regression was employed to explain the research-related covariates causing non-threshold effect. These covariates included race, internal control, assay type and study quality. Unfortunately, no satisfactory clues were found.

3.5 Quantitative Synthesis

Research without non-threshold effect should use FEM to merge data. The potential heterogeneity caused by the non-threshold effect in studies of some sample types should also

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apply REM to merge data. For miR-21 in CRC diagnosis, the pooled SEN, SPE, PLR, and NLR of blood samples were 0.71 (95% CI: 0.67–0.74), 0.78 (95% CI: 0.74–0.83), 3.53 (95% CI: 2.35–5.30), and 0.37 (95% CI: 0.27–0.49), respectively, and the pooled DOR and AUC were 10.57 (95% CI: 5.70–19.61) and 0.8447, respectively. Results of the subgroup analysis revealed that for serum samples, the pooled SEN, SPE, PLR, and NLR were 0.73 (95% CI: 0.69–0.77), 0.83 (95% CI: 0.76–0.89), 4.19 (95% CI: 2.91–6.04), and 0.30 (95% CI: 0.19–0.48), respectively, and the pooled DOR and AUC were 13.97 (95% CI: 8.44–23.11) and 0.8701, respectively; for plasma samples, the pooled SEN, SPE, PLR, and NLR were 0.67 (95% CI: 0.60–0.73), 0.76 (95% CI: 0.69–0.81), 3.11 (95% CI: 1.78–5.44), and 0.43 (95% CI: 0.29–0.64), respectively, the pooled DOR and AUC were 8.03 (95% CI: 3.30–19.52) and 0.8295, respectively; for fecal samples, the pooled SEN, SPE, PLR, and NLR were 0.33 (95% CI: 0.28–0.37), 0.91 (95% CI: 0.88–0.93), 4.77 (95% CI: 1.64–13.87), and 0.69 (95% CI: 0.51–0.93), respectively, the pooled DOR and AUC were 7.06 (95% CI: 2.17–22.95) and 0.6742. Generally, blood samples are more valuable than fecal samples for miR-21 in CRC diagnosis, and serum samples are more accurate than plasma. Table 3 shows the summary estimates of the diagnostic criteria, and Figs. 4–8 illustrate the detailed data of blood, serum, plasma and feces.

3.6 Publication bias

Publication bias is another crucial factor influencing the estimating accuracy in meta-analysis of diagnostic tests. Begg's test and Egger's test were used in this meta-analysis. The *P* values for Begg's test and Egger's test were 0.404 and 0.187, respectively, which suggest that no publication bias existed among the included studies focusing on blood samples (Fig. 9). The number of studies on fecal samples was very small for use in Begg's test and Egger's test.

4. DISCUSSION

To explore novel tumor markers for clinical applications, we performed this meta-analysis to review the values of miR-21 in different samples for systematic diagnosis of CRC. In this meta-analysis, discrepant expression levels of miR-21 in the blood, feces, and tissues showed obvious statistical significance between the CRC patients and the control individuals. For miR-21 in blood samples, the pooled SEN, SPE, PLR,
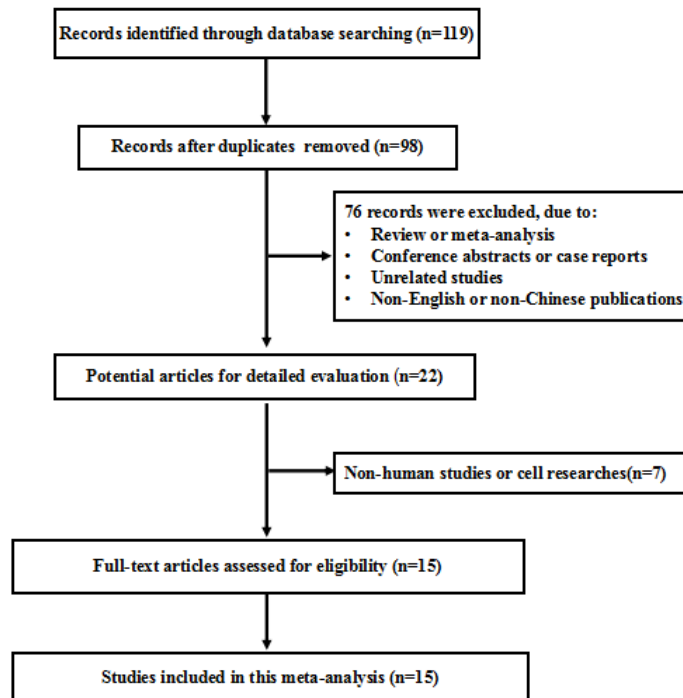

Fig. 1. The flow chart of data identification and selection

and NLR were 0.71 (95% CI: 0.67–0.74), 0.78 (95% CI: 0.74–0.83), 3.53 (95% CI: 2.35–5.30), and 0.37 (95% CI: 0.27–0.49), respectively, thus indicating prominent advantage in sensitivity and specificity of miR-21 in blood samples for the diagnosis of CRC. DOR [38] reflects the correlation between the diagnostic results and diseases. When DOR is >1, a larger value suggests better diagnostic performance. AUC [39] is used to evaluate the overall performance, and its optimal value tends to be 1. The pooled DOR and AUC of miR-21 in blood samples were 10.57 (95% CI: 5.70–19.61) and 0.8447, respectively, hence suggesting excellent performance of miR-21 in the diagnosis of CRC. In subgroup analyses, the pooled AUC, DOR, SEN, SPE, PLR, and NLR of serum samples were 0.8701, 13.97 (95% CI: 8.44–23.11), 0.73 (95% CI: 0.69–0.77), 0.83 (95% CI: 0.76–0.89), 4.19 (95% CI: 2.91–6.04), and 0.30 (95% CI: 0.19–0.48), respectively; for plasma samples, the pooled AUC, DOR, SEN, SPE, PLR, and NLR were 0.8295, 8.03 (95% CI: 3.30–19.52), 0.67 (95% CI: 0.60–0.73), 0.76 (95% CI: 0.69–0.81), 3.11 (95% CI: 1.78–5.44), and 0.43 (95% CI: 0.29–0.64), respectively. Considering the above evidence, the SEN, SPE, and overall performance of serum samples are better than that of the plasma samples, hence suggesting that anticoagulants may affect the extraction and detection of miRNAs. For fecal miR-21, the pooled AUC, DOR, SEN, SPE, PLR, and NLR were 0.6742, 7.06 (95% CI: 2.17–22.95), 0.33 (95% CI: 0.28–0.37), 0.91 (95% CI: 0.88–0.93), 4.77 (95% CI: 1.64–13.87), and 0.69 (95% CI: 0.51–0.93), respectively, indicating that fecal miR-21 exhibits favorable SPE, even though its SEN is unsatisfactory. When combined with multiple miRNAs, fecal miR-21 can decline the misdiagnosis rate of CRC. There were only 2 researches focusing on tissue miR-21 in the present study, and meta analysis was not

recommended because the result of the combined data is not persuasive. Nevertheless, both single-center studies suggested high expression of miR-21 in colorectal cancer tissue, which will provide theoretical basis for future researches on other specimen types.
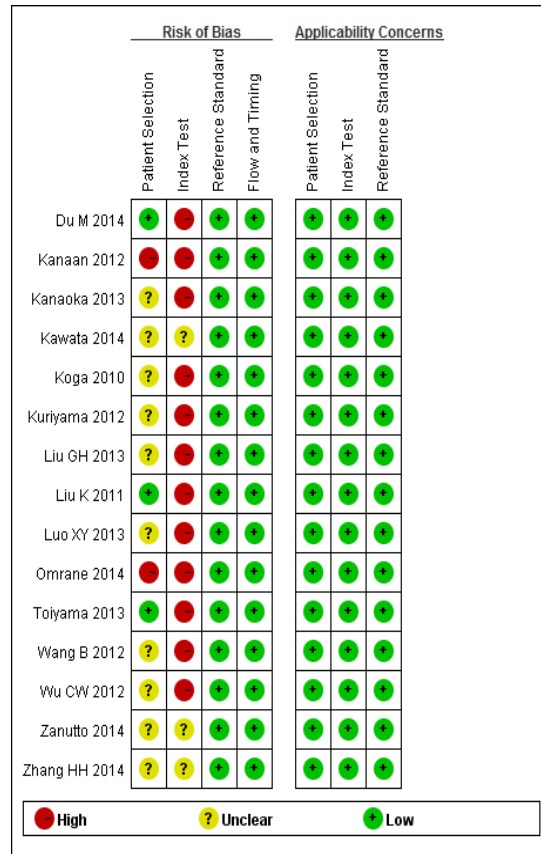

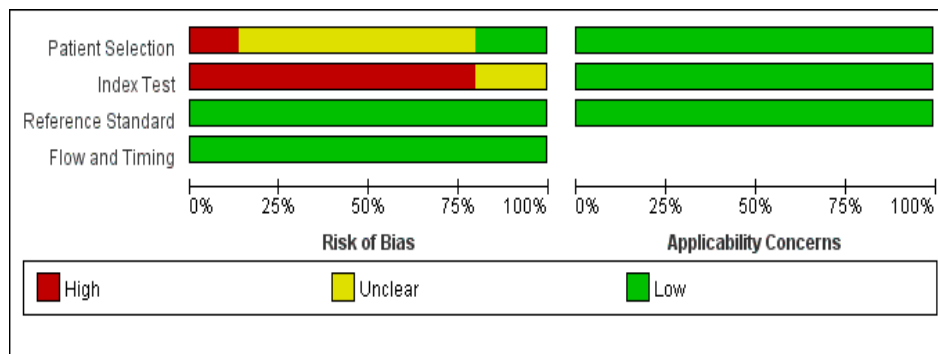**Fig. 2. Quality assessment by QUADAS-2: summary of risk of bias and applicability concern**

Fig. 3. Quality assessment by QUADAS-2: summary of risk of bias and applicability concern

Table 2. Main characteristics of included studies in this meta-analysis

Author	Year	Country	Sample size Patients: Controls	Ethnicity	Assay type (qRT-PCR)	Internal control	Specimen	SEN (%)	SPE (%)
Kawata [23]	2014	Japan	88:11	Asian	Taqman	miR-451	Serum	61.4%	90.9%
Toiyama [24]	2013	Japan	12:12	Asian	Taqman	cel-miR-39	Serum	82.8%	90.6%
Wang B [25]	2012	China	174:39	Asian	SYBR-Green	miR-16	Serum	87.5%	74.4%
Liu GH [26]	2013	China	200:80	Asian	Taqman	miR-16	Serum	65.0%	85.0%
Du M [27]	2014	China	49:49	Asian	Taqman	cel-miR-39	Plasma	76.0%	82.0%
Kanaan [28]	2012	USA	30:30	Caucasian	Taqman	RNU6B	Plasma	90.0%	90.0%
Luo XY [29]	2013	Germany	50:50	Caucasian	Taqman	cel-miR-39	Plasma	53.0%	82.0%
Zanutto [30]	2014	Italy	65:70	Caucasian	SYBR-Green	miR-16	Plasma	58.0%	58.0%
Zhang HH [31]	2014	China	41:30	Asian	Taqman	RNU6B	Plasma	51.2%	79.0%
Kanaoka [32]	2013	Japan	138:126	Asian	Taqman	RNU6B	Feces	39.9%	96.8%
Wu CW [33]	2012	China	88:101	Asian	Taqman	RNU6B	Feces	55.7%	73.3%
Koga [34]	2010	Japan	197:119	Asian	Taqman	RNU6B	Feces	14.7%	91.6%
Kuriyama [35]	2012	Japan	69:126	Asian	Taqman	RNU6B	Feces	39.0%	97.6%
Liu K [36]	2011	China	42:42	Asian	Taqman	RNU6B	Tissue	80.0%	88.2%
Omrane [37]	2014	Tunisia	25:25	African	SYBR-Green	RNU6B	Tissue	68.0%	72.0%

Table 3. Summary estimates of diagnostic criteria and the 95% confidence interval

Group	Number of studies	AUC	DOR	SEN	SPE	PLR	NLR
Tissue	2	——[a]	13.11 (2.36-72.87)	0.76 (0.64-0.86)	0.82 (0.71-0.90)	3.96 (1.39-11.30)	0.29 (0.19-0.45)
Blood[b]	9	0.8447	10.57 (5.70-19.61)	0.71 (0.67-0.74)	0.78 (0.74-0.83)	3.53 (2.35-5.30)	0.37 (0.27-0.49)
Serum	4	0.8701	13.97 (8.44-23.11)	0.73 (0.69-0.77)	0.83 (0.76-0.89)	4.19 (2.91-6.04)	0.30 (0.19-0.48)
Plasma	5	0.8295	8.03 (3.30-19.52)	0.67 (0.60-0.73)	0.76 (0.69-0.81)	3.11 (1.78-5.44)	0.43 (0.29-0.64)
Feces	4	0.6742	7.06 (2.17-22.95)	0.33 (0.28-0.37)	0.91 (0.88-0.93)	4.77 (1.64-13.87)	0.69 (0.51-0.93)

a means no AUC; at least three included studies are needed to synthesize SROC curve; b includes serum and plasma samples
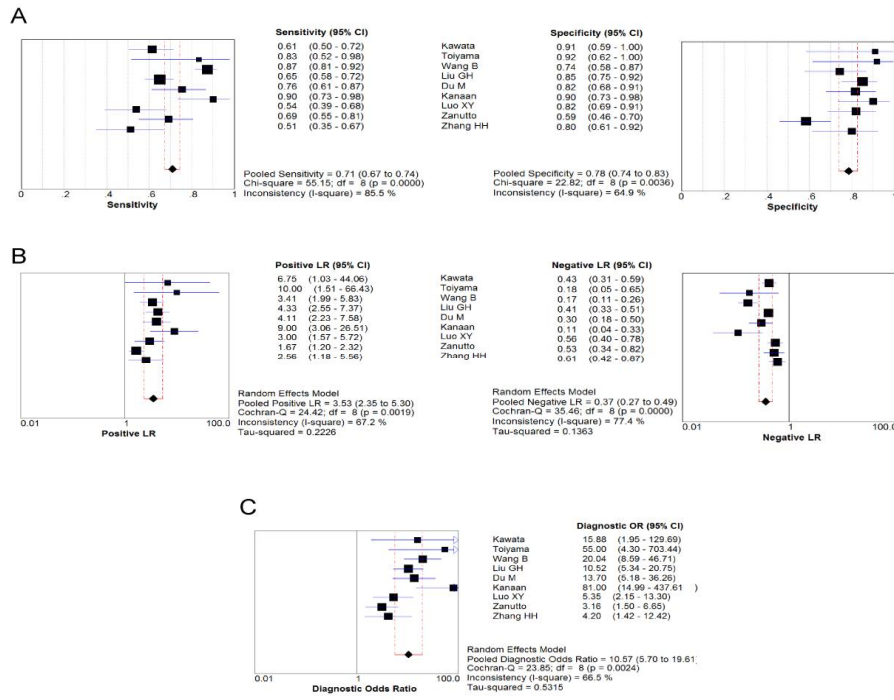
Fig. 4. The forest plots show the pooled diagnosis index of blood miR-21 for the diagnosis of CRC. The point efficiencies from each study are shown as squares, and the pooled efficiencies are shown as diamond. (A) Sensitivity and specificity; (B) PLR and NLR; (C) DOR and their 95% CI
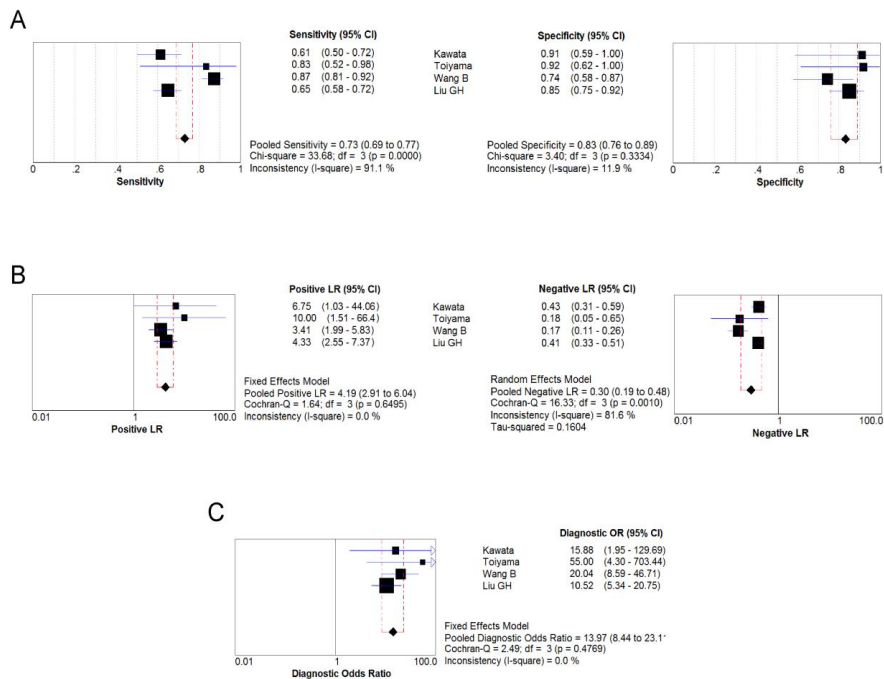

Fig. 5. The forest plots show the pooled diagnosis index of serum miR-21 for the diagnosis of CRC. (A) Sensitivity and specificity; (B) PLR and NLR; (C) DOR and their 95% CI
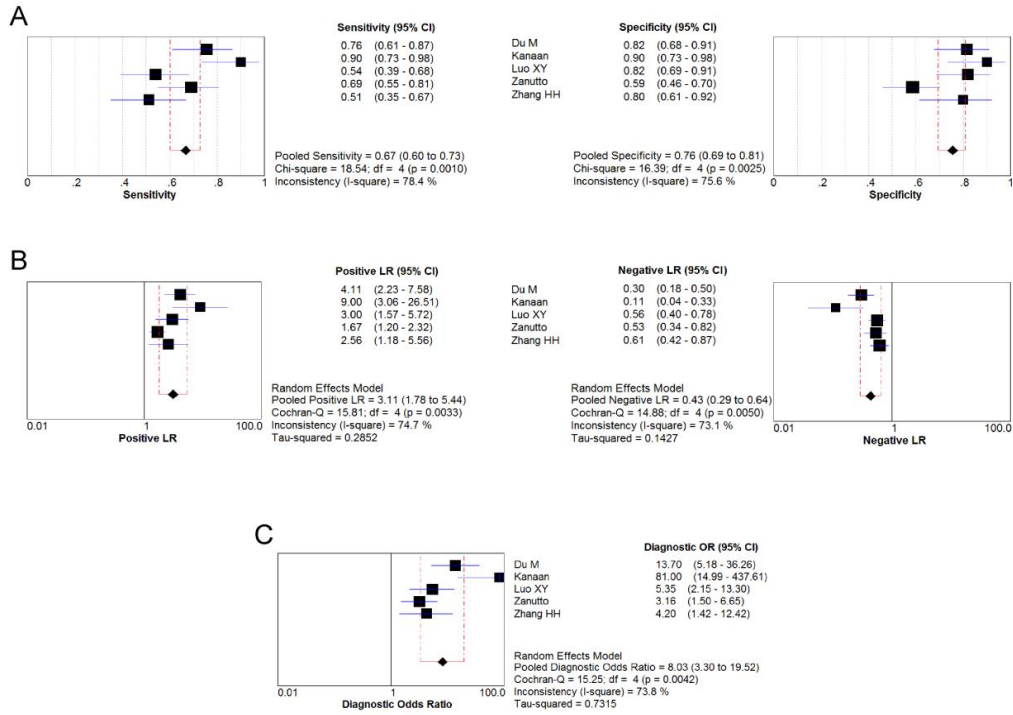
Fig. 6. The forest plots show the pooled diagnosis index of plasma miR-21 for the diagnosis of CRC. (A) Sensitivity and specificity; (B) PLR and NLR; (C) DOR and their 95% CI
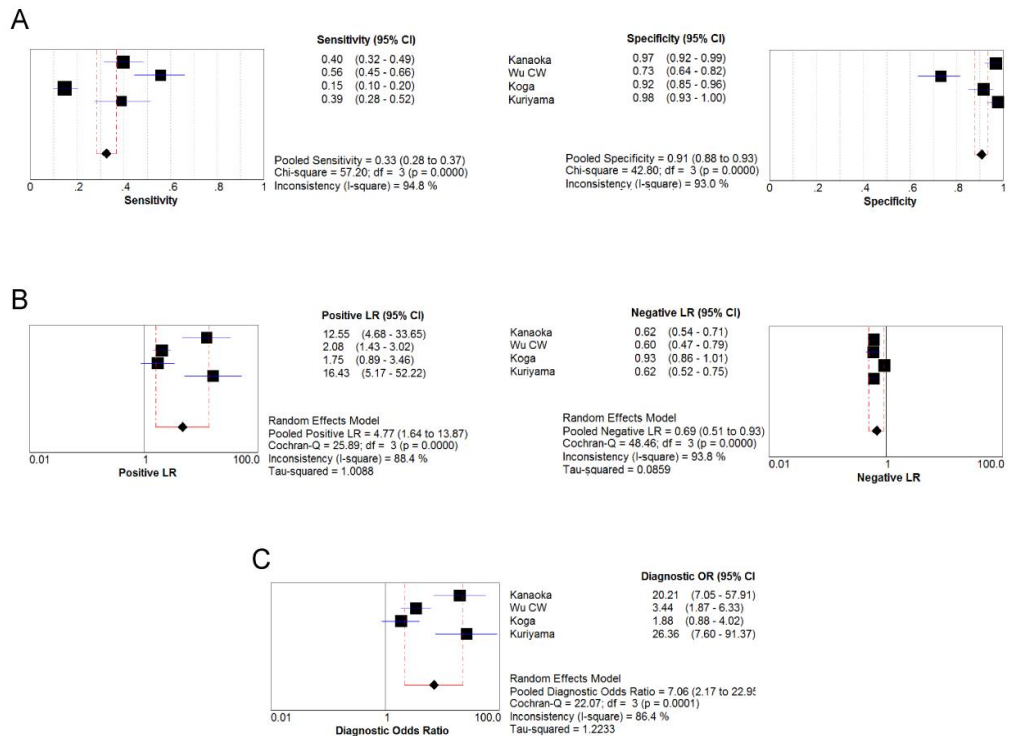

Fig. 7. The forest plots show the pooled diagnosis index of feces miR-21 for the diagnosis of CRC. (A) Sensitivity and specificity; (B) PLR and NLR; (C) DOR and their 95% CI
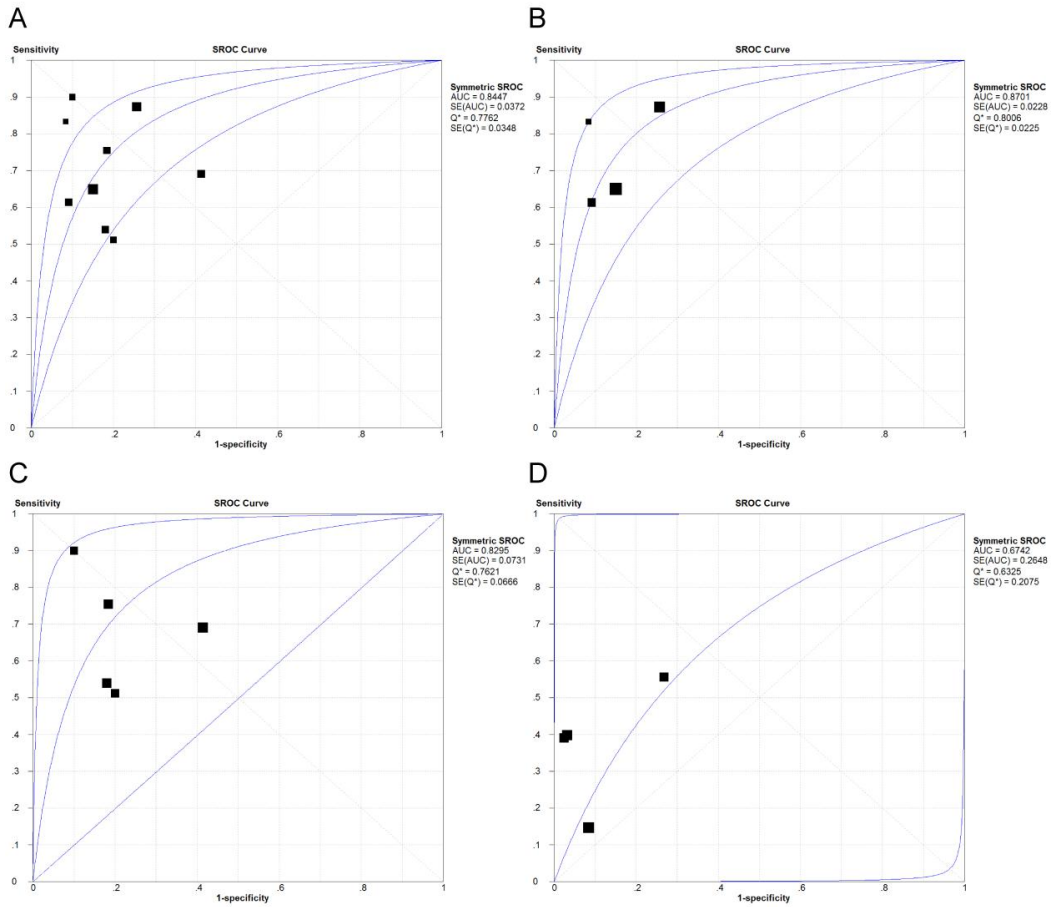
Fig. 8. Summary receiver operating characteristic curves (SROC) of miR-21 describes the diagnostic performance. (A) The SROC curve of blood is symmetric, and the AUC is 0.8447. (B) The SROC curve of serum is symmetric, and the AUC is 0.8701. (C) The SROC curve of plasma is symmetric, and the AUC is 0.8295. (D) The SROC curve of feces is symmetric, and the AUC is 0.6742
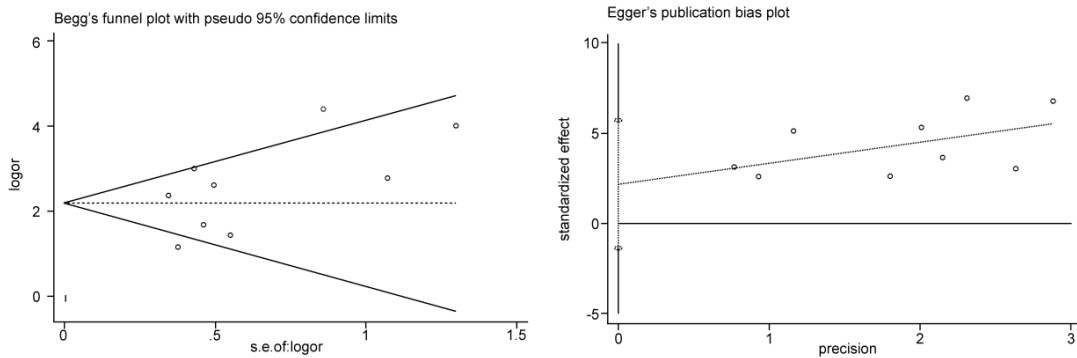

Fig. 9. Publication bias from Begg's test and Egger's test are shown by funnel plots. The line is the regression line, and every point represents one study. No publication bias is shown to exist

Some meta-analysis or systemic review articles are published in recent years on the diagnostic value of miR-21 in CRC [27,31]. All in all, the results indicated that miR-21 has a potential diagnostic value with moderate sensitivity and good specificity for CRC. Combined with our research, the diagnostic performance of miR-21 in blood samples is better than that of fecal samples, and serum samples are more beneficial than plasma for miRNA extraction and detection.

For any meta-analysis, completely avoiding the heterogeneity existing in the eligible studies [40] is indispensable; even publishers themselves prefer positive results, and publication bias thus emerges [41]. Fortunately, no threshold effect or publication bias was observed in our meta-analysis. Examination showed that non-threshold effect existed in the selected articles; however, meta-regression did not determine the responsible covariates. Hence, we combined the data by using REM to improve the accuracy of the combined results.

The prognosis of CRC patients is inversely related to tumor staging, early diagnosis, and early treatment, which can significantly decrease its mortality and recurrence. Undoubtedly, colonoscopy is a method with the maximum diagnostic performance, but it is rejected by most of patients because of its invasive nature [6]. Moreover, noninvasive examinations, including carcinoembryonic antigen [7] and FOBT [8] cannot work efficiently because of poor sensitivity and specificity. The occurrence, staging, metastasis, and recurrence of CRC are closely related to the abnormal expression of miRNAs, and their stable existence in serum, plasma [9,10], and feces [11] has facilitated clinical applications of miRNAs. Furthermore, our meta-analysis demonstrated that miR-21 in the blood yields preferable performance in the diagnosis of CRC; fecal miR-21 exhibits satisfactory specificity, and it can reduce the misdiagnosis rate in cooperation with other indicators. This evidence suggested that miR-21 is a potential powerful biomarker in CRC diagnosis.

Although its results are promising, this meta-analysis still has limitations. First, miR-21 has only recently emerged as a novel marker in CRC diagnosis, thus, our meta-analysis only includes a small sample size. Therefore, further validations of miR-21 in large cohort and independent studies are needed. Second, many other cancer types dysregulate miR-21. However, studies that distinguish CRC from other cancer types are lacking, which may limit the application of miR-21 in clinical settings. Further comprehensive studies are needed to solve this problem. Furthermore, the detecting methods for miRNAs are all based on qRT-PCR. Unified primers and reference miRNAs for qPCR analysis remain unavailable to date.

5. CONCLUSION

In conclusion, our research demonstrated that miR-21 in blood samples has better diagnostic performance than that in feces, and serum samples are even better for the detection of miR-21. Fecal miR-21 exhibits favorable specificity but with poor sensitivity. However, several limitations exist in this meta-analysis. First, the implementation of the gold standard did not meet the requirements of the blind method; second, case selection did not strictly abide the continuous random inclusion; finally, small sample size was used in some selected studies. Consequently, blind-designed random studies in large scale should be strictly conducted by multi-center medical institutions locally and internationally to achieve more authoritative results.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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