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Meta-Analysis

A meta-analysis of microRNA-17 as a potential biomarker in diagnosis of colorectal cancer

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Abstract: This meta-analysis was aimed to determine the diagnostic accuracy of circulating microRNA-17 for colorectal Cancer (CRC). Databases including PubMed, Embase, Web of Science, Cochrane Library and China National Knowledge Infrastructure (CNKI) were searched up to February 23, 2018 for eligible studies. Quality Assessment of Diagnostic Accuracy Studies (QUADAS) was employed to assess the quality of the included studies. Meta-analysis was performed in STATA 13.0. Ten studies with total 938 CRC patients and 638 control individuals were included in this meta-analysis. All of the included studies are of high quality. The summary estimates revealed that the pooled sensitivity is 0.75 (95% confidence interval (CI): 0.60–0.85) and the specificity is 68% (95% CI: 0.56–0.77), for the diagnosis of CRC. In addition, the area under the summary ROC curve (AUC) is 0.76. The current evidence suggests that circulating miR-17 has the potential diagnostic value for CRC. More prospective studies on the diagnostic value of circulating miR-17 for CRC are needed in the future. Together, microRNA-17 might be a novel potential biomarker in the diagnosis of colorectal cancer, and more studies are needed to highlight the theoretical strengths.

Key words: MicroRNA-17; Colorectal cancer; Diagnosis; Meta-analysis.

Introduction

Colorectal cancer (CRC) is one of the most common digestive system neoplasm. Its mortality ranks the third among all common tumor (1). The occurrence of CRC is occult, and most of the early CRC patients have no obvious symptoms. At present, colonoscopy was currently considered to be the "gold standard" for the early diagnosis of CRC. However, colonoscopy is difficult to universal use as an early screening method for CRC due to the trauma, high economic burden, relying so heavily on the doctor's technical experience, and its risk of intestinal perforation. The fecal occult blood test (FOBT) is also difficult to generalize, but because of its low sensitivity and low specificity. Finding a simple, economical method for CRC is currently urgently needed. Numerous studies are currently exploring molecular markers that can be used to detect CRC.

MicroRNA (miRNA) is a 22-nt-long non-coding RNA that negatively regulates the expression of target genes by binding to 5-8 bases of the 3'-UTR region of the target gene RNA(2). Studies have shown that miRNAs expression is significantly varied from tumor tissue and normal tissue (3). MiRNA involved in a variety of biological processes, studies have confirmed that miRNA participates in development, cell differentiation, cell apoptosis and tumorigenesis (2). MiRNAs are relatively stable in biological samples (such as blood and feces). The tumor-associated miRNAs have been also detected in the blood from cancer patients (4, 5). Different kinds of cancer have distinct miRNA profiles (6). Finding the appropriate miRNA as a tumor marker for the early diagnosis of CRC was the current research direction. Recently, it has been reported in the literature that the miR-17~92 cluster is involved in the development and progression of colon cancer and expressed in colon cancer tissues. It is suggested that the miR17~92 cluster may be involved in the development of colon cancer (7, 8). In 2009, Ng et al (9) analyzed 95 miRNAs and identified miRNA(miR)-17 as exhibiting the most significant overexpression in the plasma and tumor tissues of colon Cancer patients. Humphreys KJ et al reported that the homeostatic function of miR-18a within the miR-17~92 cluster in colorectal cancer cells may be achieved through suppression of CDC42 and the PI3K pathway (10). Fang. Li et al demonstrated that miR-17-5p promotes chemotherapeutic drug resistance and tumor metastasis of colorectal cancer by repressing PTEN expression (11). However, a later study found no significant differences between miR-17 levels in the serum of CRC patients and heathy controls (12). To understand whether the miR-17 servers as a diagnosis biomarker for CRC, we did the system review and meta-analysis by using pool of published literatures searched from several authoritative electronic databases without constraints on publication date. The inception of data sources was published at February 23, 2018. Our data showed that miRNA-17 may be a novel potential biomarker in the diagnosis of colorectal cancer.

Materials and Methods

Search Strategy

We carried out a comprehensive search strategy in various databases including PubMed, Embase, Web of Science, Cochrane Library and China National

Knowledge Infrastructure (CNKI) to seek out the articles up to February 23, 2018. No restriction was used on language, year of publication and publishing status. The keywords employed in the literature retrieval included: "microRNA-17" or "miR-17" or "miRNA-17" or "hsa-miR-17" and "colorectal cancer" or "colorectal tumor" or "colorectal neoplasms" or "colorectal carcinoma". In addition, we also manually searched the references from included articles and relevant published reports.

Inclusion and Exclusion Criteria

All of the studies were carried out based on a careful study of title and summary, and full texts were found for any potential qualifications. Any disagreement was resolved through thorough discussion. Inclusion criteria: (1) The diagnosis of CRC requires colonoscopy or histological examination; (2) The control group matched to an experimental group showed negative colonoscopy in the recent absence and none had a history of any type of cancer; (3) All blood samples were collected prior to colonoscopy without any treatment; (4) The included studies should include sensitivity , specificity (or derived from the data the likelihood of these values), and a well-defined cut-off value; (5) The number of cases and controls included in the study was greater than 20; (6) The data onto miR-17 in inclusion studies were independent data. Exclusion Criteria: (1) Duplicate publications; (2) Letters, editorials, meeting abstracts, case reports and reviews; (3) Unqualified patients and control subjects; (4) Insufficient data. If the same authors reported their results acquired from the overlapping population or multiple published data on the different works, only the nearest or the most complete report was included.

Data Extraction

Two investigators perused the full texts of included studies and extracted the following data independently: authors, country, journal, year of publication, study design, number and characteristics of patients and controls respectively, test method, RNA extraction kits, sensitivity, specificity and so on. Disagreements were solved by fully discussing with the third senior investigator to reach a consensus.

Quality Assessment

The quality of each study was assessed independently by two investigators according to the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2). The QUADAS-2 is recognized as an improved, redesigned tool which comprises 4 key domains (patient selection, index test, reference standard, and flow and timing) supported by signaling questions to aid judgment on risk of bias, rating risk of bias and concerns about applicability as "high", "unclear" and "low"(13).

Statistical Analysis

All statistical analyses were performed by STATA 13.0 statistical software. All accuracy data from each study (true positives, false positives, true negatives and false negatives) were extracted to obtain pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predicted value, negative predicted value, diagnostic odds ratio (DOR) and their 95% confidence interval [95% CI], simultaneously, generate the summary receiver operator characteristic (SROC) curve and calculate the area under the curve (AUC). The sensitivity, specificity, positive and negative predicted value, and diagnostic odds ratio of miR-17 were presented as forest plots. Moreover, the heterogeneity between the studies caused by threshold effect was quantified using Spearman correlation analysis. The Non-threshold effect was assessed by the Cochran-Q method and the test of inconsistency index (I^2), and a low p value (≤0.05) and high I^2 value (≥50%) suggest presence of heterogeneity by caused Non-threshold effect. If the Non-threshold effect existed, meta-regression would be used to find out the sources. For publication bias, all eligible studies were assessed Egger's test using STATA 13.0 statistical software. The *P* value with less than 0.05 shows a result of statistical significance.

Results

Data Selection

One hundred and eighty-one literatures were primitively identified according to the literature search strategy from databases (PubMed, EMBASE, Web of Science, Cochrane, CNKI) (Fig.1). Following read the titles and abstract of these articles, 82 duplicates were removed. Of these remained 99 literatures, their full-text versions were retrieved. Of these, 8 articles were reviews, 13 were animal researches, 27 were do not conform to the research purpose, so all 48 of these articles were excluded from further analysis. 51 l articles were considered to be potentially eligible were retrieved for full text perusal. Among the 40 articles were excluded from further analysis due to no result of diagnose or incomplete data. Thus, 11 studies met for this systematic review (9, 14-23), 2 of them were excluded with reasons that cannot extract complete data (5, 9), finally 9 articles (included 10 studies) were included in meta-analysis.

Study Characteristics

All of these eligible literatures were published from 2010 to 2018, accumulating 938 CRC patients and 688

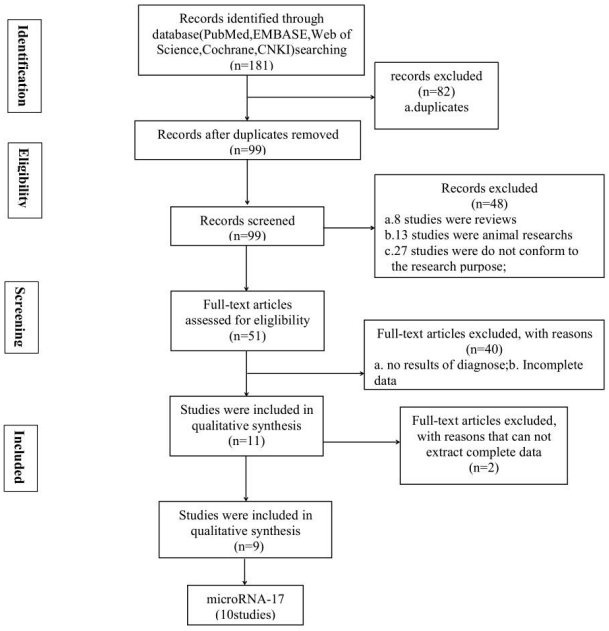

Figure 1. Flow chart of the study selection.7

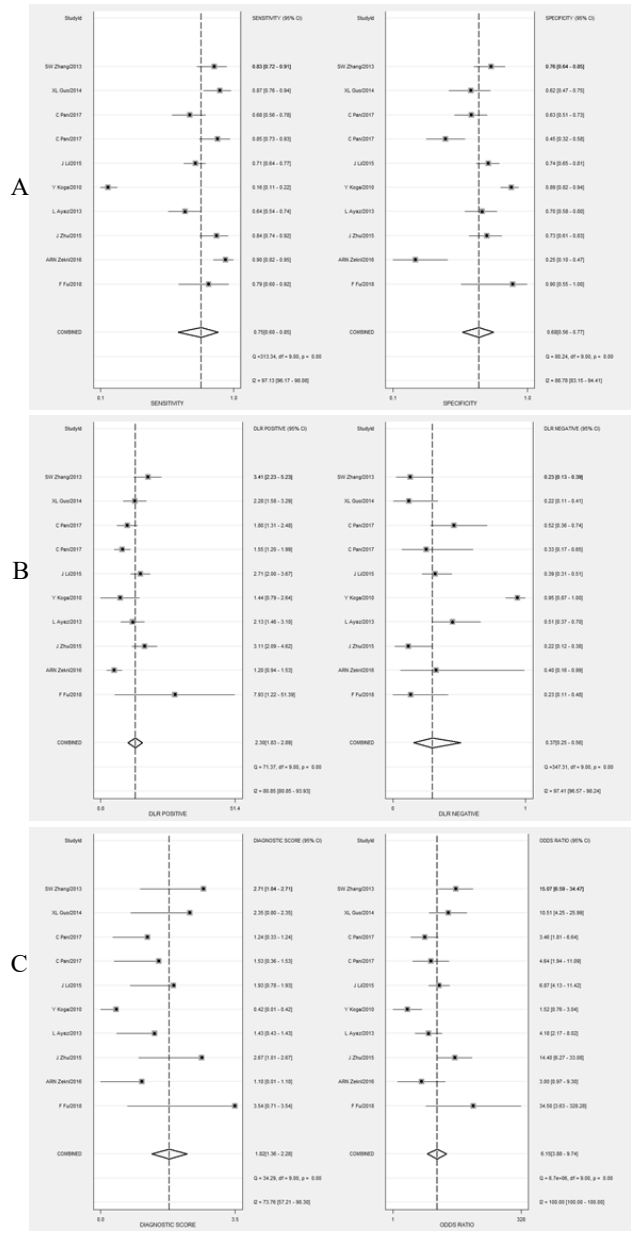

Figure 2. The forest plots show the pooled diagnosis index of miR-17 for the diagnosis of CRC. The point efficiencies from each study are shown as squares and the pooled efficiencies are shown as diamond. Degree of freedom is abbreviated as df. Inconsistency is used to quantify the heterogeneity caused by non-threshold effect. Of these studies, random effects model was used to pool these data. (A) Sensitivity and specificity, (B)PLR and NLR, (C) DOR, and their 95% CI are displayed respectively, which suggests miR-17 might be a potential noninvasive diagnosis biomarker of CRC.

healthy controls. Colonoscopy was considered as gold standard to diagnose the CRC. The study characteristics, including the first author, publish year, country, the numbers of patients and controls, TNM stage, RNA extraction kits, test method, location, sample, sensitivity, specificity and AUC, are listed in Table 1.

Quality Assessment

The quality of the included studies was assessed using QUADAS-2 quality assessment (13). As shown in table 2, all of the 9 inclusions are belonged to upper middle quality. However, a major bias was found in these included studies. In general, the major biases of these eligible studies were concentrated upon the "patient selection", because a case-control design was not avoided.

The quality of the research included is assessed by quality assessment QUADAS-2. As shown in table 2, the nine studies are medium quality. However, a major bias was found in these studies. In general, these eligible studies tend to be "patient selection", since case-control design cannot be avoided.

Heterogeneity and Threshold Effect

The heterogeneity between the studies is a critical key to understand the possible factors that influence accuracy estimates, and to evaluate the appropriateness of statistical pooling of accuracy estimates from various studies (24). In the present study, the representation of the sensitivity against the specificity of each study is shown in an SROC curve (25) (Fig.3), which can be used to detect the threshold effect. In order to assess whether the heterogeneity of miR-17 is amongst the eligible studies, we first calculated the correlation coefficient and P value between the logit of sensitivity and logit of 1-specificity by using Spearman test to exclude the threshold effect. As a result, the Spearman correlation coefficient was 0.612 and the *P* value was 0.06 (>0.05), indicating that there was no heterogeneity from threshold effect. Due to the non-threshold effect being another key to the heterogeneity between the studies, the inconsistency index (I^2) was employed. The I^2 in the forest plot of diagnosis index was more than 50% (as shown in Fig.3) that suggested the heterogeneity caused by non-threshold effect was existed among these studies.

Data Analysis

Because of the potential heterogeneity caused by non-threshold effects of these studies, we used the random effects model in our study to estimate the overall performance of miR-17 in CRC diagnosis. Forest plots show 10 sensitivities, specificities, PLR, NLR, and DOR values for the miR-17 study in this study (Fig.2).

Heterogeneity in sensitivity and specificity was detected in the 10 studies (I^2=97.13%, *P*=0.00 and I^2=88.78%, *P*=0.00 respectively), suggesting significant heterogeneity in sensitivity and specificity (Fig. 2A). A pooled sensitivity and specificity of miR-17 were 0.75 (95% CI: 0.60–0.85) and 0.68 (95% CI: 0.56–0.77) in the diagnosis of CRC patients, respectively (Fig.2A). Its PLR in diagnosis CRC was 2.30 (95% CI: 1.83–2.89), indicating that the case groups have more than a two-fold probability to express miR-17 in comparison to control individuals. Its NLR in diagnosis CRC was 0.37 (95% CI: 0.25–0.56) (Fig.2B). The summary DOR (Fig.2 C) was 6.15 (95% CI: 3.88–9.74), indicating that miR-17 can be used as a good marker for CRC diagnosis. The area under the SROC curve (AUC) was 0.76, suggesting a moderate diagnostic accuracy of miR-17 for CRC diagnosis (Fig.3). Likelihoods dot plots (Fig.4) were found in the four quadrants. Among the 10 studies included, there were 4 studies (14, 16, 22, 23) in the upper left quadrant, 1 studies (19) in the upper right quadrant, and 1 studies (20) in the lower left quadrant, 4 studies (9, 15, 18, 20) in the lower right quadrant.

Meta-regression

Because the heterogeneity generated by non-thres-

Table 2. Main characteristics of the eligible studies.

Author	Year	Country	Ethnicity	RNA extraction kits	Test method	Patients	Control	TNM(I/II/III/IV)	Location		Sample	AUC	Se(%)	Sp(%)	Se and Sp estimation
Fu et al (14)	2018	China	Asian	HiPure Liquid RNA/ miRNA	RT-qPCR (SYBR-Green)	29	10	2/2/9/5/11*	14	15	Serum	0.90	80	86	Data extrapolated
Zekri et al (15)	2016	America	Caucasian	miRNeasy Mini	RT-qPCR (SYBR-Green)	100	24	NR	NR	NR	Serum	0.81	90	25	Data extrapolated
Zhu et al (16)	2015	China	Asian	miRNeasy Mini	RT-qPCR (Taqman)	70	70	14/56/0/0	NR	NR	Serum	NR	84	73	Reported in text
Ayaz et al (9)	2013	China	Asian	miRNeasy Mini	RT-qPCR (SYBR-Green)	90	75	6/34/23/27	NR	NR	Plasma	0.72	64	70	Reported in text
Koga et al (18)	2010	Japan	Asian	miRNeasy Mini	RT-qPCR (Taqman)	197	119	NR	NR	NR	Fecal	NR	16	89	Reported in text
Li et al (19)	2015	China	Asian	Trizol-LS	RT-qPCR (Taqman)	175	130	0/101/75/0	74	102	Serum	0.78	71	74	Data extrapolated
Pan et al (20)	2017	China	Asian	RNA isolation	RT-qPCR	60	60	12/17/24/7/0#	31	29	Serum	0.68	85	45	Reported in text
Pan et al (20)	2017	China	Asian	RNA isolation	RT-qPCR	80	80	8/27/29/11/5#	50	30	Serum	0.66	68	63	Reported in text
Guo et al (22)	2014	China	Asian	NR	RT-qPCR	67	50	12※/33/22	NR	NR	Serum	0.91	87	62	Reported in text
Zhang et al (23)	2013	China	Asian	Trizol-LS	RT-qPCR (Taqman)	70	70	NR	NR	NR	Serum	0.62	83	76	Reported in text

*distant metastasis #unknown by TNM stage ※Individuals of Iand II were not specified by TNM stage. NR: not report; Se: sensitivity; Sp: specificity; AUC: the area under the curve.

Table 3. QUADAS-2 assessment for the eligible studies.

Study	F Fu 2018	ARN Zekri 2016	J Zhu 2015	L Ayaz 2013	Y Koga 2010	J Li 2015	C Pan 2017	XL Guo 2014	SW Zhang 2013
(1) patient selection	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
1.Was a consecutive or random sample of patients enrolled?	N	U	U	N	U	U	U	U	U
2.Was a case-control design avoided?	N	N	N	N	N	N	N	N	N
3.Did the study avoid inappropriate exclusions?	Y	Y	Y	Y	Y	Y	Y	Y	Y
(2) index test	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
1.Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.If a threshold was used, was it pre-specified?	Y	Y	Y	Y	Y	Y	Y	U	Y
(3) reference standard	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
1.Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.Were the reference standard results interpreted without knowledge of the results of the index test?	Y	Y	Y	Y	Y	Y	Y	Y	Y
(4) flow and timing	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
1.Was there an appropriate interval between index test(s) and reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.Did all patients receive a reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.Did patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.Were all patients included in the analysis?	Y	Y	Y	Y	N	Y	Y	Y	Y

Y, Yes; U, Unclear; N, No.

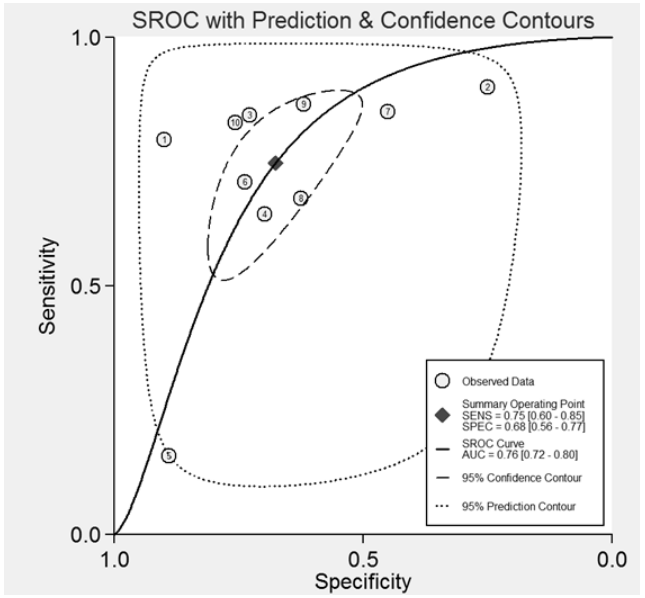

Figure 3. Summary receiver operating characteristic curves (SROC) of miR-17 describes the diagnostic performance.

hold within the studies can be obviously observed in the forest plot of diagnosis index (as shown in Fig.3), we attempted to explain this heterogeneity by exploring the study characteristics, such as age, TNM stage, specimen numbers, using meta-regression. The country, ethnicity, the different kinds of samples and the stage of CRC patients may cause of the heterogeneity. Meta-regression analysis suggests that the country (p=0.26), the ethnicity (p=0.65), the stage of CRC patients (p=0.09) and the different kinds of sample (p=0.99) are not the sources of heterogeneity in this study. Unfortunately, no satisfactory clues were found.

Publication Bias

The publication bias is recognized as another influent factor to the diagnosis accuracy. Egger's test was used in this meta-analysis. The P value is 0.419 for Eegg's test, which is more than 0.05 and suggests no publication bias exist among these included studies (Fig.5). However, concluding whether or not publication bias exists is difficult due to the limited number of studies involved in the current meta-analysis.

Discussion

This study was the first to evaluate the significance of miR-17 as a tumor marker for CRC in an evidence-based manner. This study found that the differential expression of miR-17 in CRC patients compared with the control group was statistically significant. AUC is the combined statistic of the SROC curve. It does not depend on the diagnostic threshold and is considered to be the overall test performance. The AUC of a good diagnostic test is close to 1, and the AUC of a test with no diagnostic accuracy is close to 0.5 (26). Diagnostic odds ratio (DOR) is used as an indicator of compactness between diagnosis efficiency and cases. It is used to indicate that the chance of positive results of diagnostic tests is a multiple of negative results. It has excellent test performance and its accuracy is stable (27). In this study, we combined the combined sensitivity and specificity, positive likelihood and negative likelihood ratio, DOR and other indicators, combined with the AUC results in the fitted SROC curve, suggesting that miR-17 as a diagnostic biologic for CRC. The marker, miR-17, has potential diagnostic value for diagnosing CRC with moderate diagnostic accuracy.

To analyze the sources of heterogeneity in this study, the heterogeneity test results showed that there was no heterogeneity due to threshold effects in this meta-analysis, but there was heterogeneity due to non-threshold effects. Meta-analysis was used to analyze the grades and biological samples of patients from countries, races, and CRCs. The results showed statistical significance, indicating that the above indicators were not the sources of heterogeneity in this study. Studies have found that if the articles included in the meta-analysis are all published studies, it will have a certain adverse effect on the research results. This is because the research hotspots and results tend to cater to the results already obtained (28). Analysis of the study's choices did not reveal publication bias. The analysis of the study's likelihood was compared with the 10 studies found in the four quadrants of the dot plot. The upper left quadrant indicates that the diagnosis can be diagnosed and excluded. The upper right quadrant indicates that the diagnosis can be confirmed. The lower left quadrant indicates that the diagnosis can be excluded. The lower right quadrant indicates that neither diagnosis nor diagnosis can be ruled out. Therefore, it shows that miR-17 has a certain diagnostic value for the diagnosis of colon cancer, there are also some limitations.

The important role of miRNAs in the development, progression and metastasis of cancer (2, 6). With the

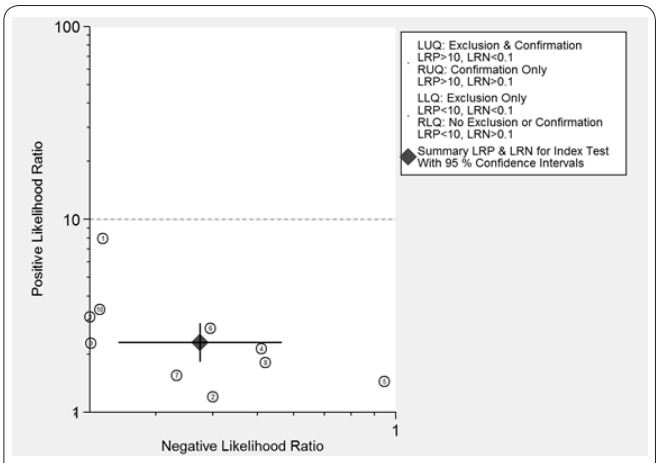

Figure 4. Likelihoods dot plots.

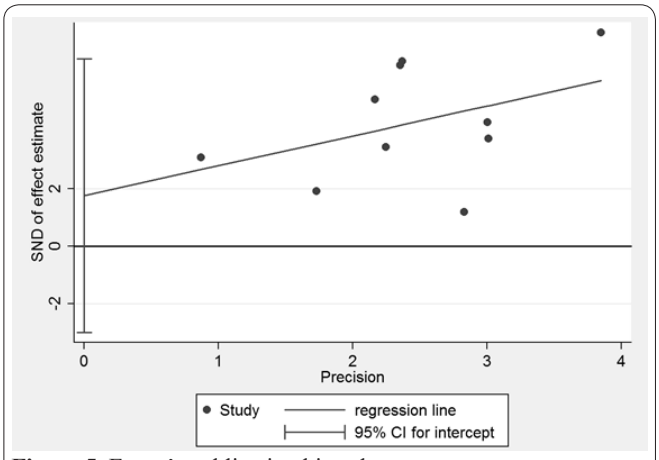

Figure 5. Egger's publication bias plot.

deepening of miRNA research, the relationship between colon cancer and miRNA has drawn increasing attention. Studies have reported that miR-17~92 clusters are dysregulated in colon cancer tissues. This suggests that miR-17~92 clusters may be involved in the development and progression of colon cancer (29, 30). In 2009, Ng et al (4) 95 miRNAs and identified miR-17 as exhibiting the most significant overexpression in the plasma and tumor tissues of CRC patients. The marker, miR-17, has several distinct advantages. MiR-17 is expressed stably in the human body. Studies have found that miRNAs can enter the circulatory system, including blood and other body fluids (31, 32), which are presumably released from broken cells (33), and detect biomarkers in the microenvironment that are involved in tumor metastasis as a key role (34). CRC is a highly curable disease. Early diagnosis and early treatment are of great significance. The method for detecting miR-17 in the human microenvironment mentioned in this study is simple, economic, and easy to implement. There are significant advantages in detecting compliance and noninvasiveness in the microenvironment (34). Our meta-analysis stimulated the differential expression of individual miRNAs in plasma to distinguish CRC from normal people, which increased the possibility of using this marker to develop future non-invasive and rapid diagnostic tests for CRC.

Studies have confirmed that miR-17 is also highly expressed in many tumors. If discovery the overexpression of circulating miR-17, the diagnostic of CRC should be further confirmed by other pathological features. Although miR-17 is not unique as a biological marker for early CRC diagnosis, it can be used as a directional index, abnormal expression of miR-17, and its combined sensitivity.At 0.75, the post-merger specificity was 0.68, suggesting that miR-17 is highly sensitive compared to the existing clinical test FOBT (35). Although our results are promising, this meta-analysis has limitations. There are fewer miR-17 articles included in this study, so it is necessary to strengthen our conclusions by further verification of miR-17. In addition, studies have confirmed that miR-17 is also highly expressed in many tumors. Although miR-17 is not a unique biomarker of early CRC diagnosis, it can be used as a directional marker to establish diagnostic CRC biomarkers. This study provides research directions for improving the diagnostic sensitivity and specificity of CRC.

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