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ORIGINAL ARTICLE

Evaluation of serum miR-21, miR-29, miR-92, miR-135, miR-210, and miR-1290 biomarkers for diagnosis of colorectal cancer using systematic review and meta-analysis study

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ABSTRACT

A significant mortality is attributed to a common cancer called colorectal cancer (CRC), and current screening methods for CRC could be improved. Circulating microRNAs (miRNAs) have been identified as promising diagnostic biomarkers in body fluids by their rearrangement between healthy and diseased individuals. This study reviewed studies on miRNAs to investigate their use as screening tools for CRC diagnosis.

We searched PubMed, Scopus, and Web of Science (WoS) databases to discover and find relevant miRNAs that could be used as diagnostic biomarkers in CRC. Patient number and demographic characteristics, patient sample type, miRNA detection method, normalization type, and significantly dysregulated miRNAs were recorded. Meta-analysis was performed across studies with similar dysregulated miRNAs. Initially, 1207 identified articles were entered into ENDNOTE, of which 422, 393, and 392 were from Scopus, WoS, and PubMed, respectively. After reviewing and screening studies by two researchers separately and removing duplicates and irrelevant ones, 126 articles remained as final articles. In the meta-analysis, 6 distinct miRNAs including miR-21, miR-29, miR-92, miR-135, miR-210, and miR-1290 were identified in 42 studies. To evaluate the diagnostic accuracy of these miRNAs in colorectal cancer, Forest plots were drawn and statistical analysis was performed using the area under the ROC curve (AUC), sensitivity (95% CI), and specificity (95% CI).

The results showed that the identified miRNAs discriminated colorectal cancer (CRC) patients from healthy individuals with high sensitivity and specificity and outperformed conventional tumor biomarkers, making miRNAs a potential blood-based marker for colorectal cancer diagnosis.

Keywords: Colorectal cancers, Biomarkers, Early diagnosis, MicroRNAs, Meta-Analysis

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Introduction

Universally, the fourth major reason of deaths caused by cancer is attributed colorectal cancer (CRC), and it is the third and the second most cancer occuring in men and women, respectively.(1) Although the mortality and incidence rates of CRC are different widely worldwide, It is predicted that the burden will rise by 60%, and there will be greater than 2.2 million new cases and 1.1 million deaths until 2030 (2). Many factors increase the risk of CRC such as age, family history, diet or lifestyle, and inflammatory bowel diseases, and genetic disorders play only a minor role in this disease. (3).

Three genetic factors affect in the development of CRC, such as chromosomal, microsatellite, and epigenetic instabilities, which cause two critical multistep morphological pathways, including the conventional concept of adenoma-carcinoma and serrated neoplasia (4, 5). It is crucial to note that approximately 70% of diagnosed subjects are symptomatic patients without screening who are discovered in the late stage of the disease (6). Currently, a variety of noninvasive to invasive CRC screening methods are available marked by distinct benefits and disadvantages. Fecal immunochemical test, fecal occult blood test, flexible sigmoidoscopy, and colonoscopy are techniques for diagnosis of CRC. Each of these methods has specific cons and pros; for example, fecal tests detect preneoplastic lesions with low sensitivity and have a high false-positive rate, while colonoscopy are invasive diagnostic method (7).

As a potential diagnostic tool, different blood-based biomarkers have been developed to improve CRC screening tests.A traditional biomarker, Carcino embryonic antigen (CEA), is commonly used for the recurrence of CRC but it is not

suitable for diagnosis because of its low sensitivity and specificity (8). The Food and Drug Administration (FDA) has confirmed that the Methylated Septin9 assay is the first noninvasive blood test to screen patients for CRC, but the detection of adenomas or polyps is limited by its sensitivity (9).

Consequently, to aid in the early diagnosis, prognosis, and treatment of CRC, identifying novel biomarkers that are noninvasive and have high sensitivity and specificity is necessary. MicroRNAs (miRNAs) are a category of small (18–22 nucleotide) non-coding RNAs that target mRNAs to regulate gene expression after transcription (10). MiRNAs have been found to play a significant role in several different biological and pathological processes such as cell growth, migration, invasion, and metastasis (11). Furthermore, miRNAs are capable of regulating the tumor microenvironment, influencing tumor-stromal interactions, tumor angiogenesis, and immune system (11, 12).

After investigating circulating miRNAs, many researchers focused on their roles as cancer-specific biomarkers. MiRNAs have been identified in different fluids, such as serum, plasma, saliva, urine, tears, cerebrospinal fluid (CSF), seminal fluid, extracellular fluid, and others fluids of the body (13). The stability of miRNAs in circulation is remarkable due to their protection against endogenous RNases through various protective processes (14).

miRNAs present in body fluids can be attributed to three main pathways: (1) cell apoptosis, which causes passive influx of cellular miRNAs into the circulation (2) active secretion by microvesicles and exosomes (3) active selective secretion (15).

Therefore, it was found that circulating miRNAs are a suitable miRNA index of primary tumors or metastatic lesions, helping to non-invasive detect tumors at different stages. Given the conceivable of miRNAs as invaluable biomarkers in CRC diagnosis, we systemically reviewed studies which had introduced circulating miRNAs (plasma or serum or saliva) for the diagnosis of CRC.

Methods

Searching

Initially, a search strategy was designed using appropriate keywords to find miRNAs associated with colorectal cancer diagnosis, as shown in Supplementary Table 1. The search in PubMed, Scopus and Web of Science (WoS) databases was initiated on July 25, 2023 and continued until December 2025 due to the numerous studies and meta-analyses performed, with new studies being added to the review regularly.

References obtained from the databases were included in EndNote software and in the first step, duplicate studies were removed. The studies were then screened separately by two researchers (AK and MMT) based on eligibility criteria, title and abstract. If there was a disagreement on a specific issue, the other two authors (AM and SA) discussed and resolved it.

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Inclusion criteria

All cohort, cross-sectional, or case-control studies that identified miRNAs in body fluids from human samples regardless of sex and age and that contributed to the early diagnosis of CRC were included in this systematic review. There were no restrictions on the publication date and language of the studies. The gold standard screening test in the studies for the diagnosis of CRC was colonoscopy and pathology. In vitro studies on cell lines and animal studies were excluded from the review.

Risk of bias assessment and data extraction

The Newcastle-Ottawa (NOS) assessment checklist was selected to assess the risk of bias. This checklist includes: 1) Is the case definition adequate?, 2) Representativeness of the cases, 3) Selection of Controls, 4) Definition of Controls, 5) Comparability of cases and controls on the basis of the design or analysis, 6) Ascertainment of exposure, 7) Same method of ascertainment for cases and controls, 8) Non-response rate, which evaluates our studies in terms of distinguishing control and CRC groups in differences in miRNA(s) expression and a score of ≥6 was considered as good quality studies (Supplementary Table 2).

Variables including the name of the first author, year of publication, type of study design, country, number of subjects, patient characteristics including race, gender, age, type of biological sample studied, method of miRNA measurement, type of miRNAs and type of change (increase or decrease) in each study, sensitivity and specificity and area under the ROC curve (AUC) were extracted.

Any disagreements in data extraction and quality assessment up to this point were resolved between the two researchers through consultation and consensus.

Heterogeneity Assessment

Statistical heterogeneity, which refers to the difference in the results of individual studies, was assessed using the Chi-square (Chi^2) test at a statistical level of 5%. Heterogeneity was also quantified using the I^2 statistic and variance between studies was assessed using the Tua-squared statistic (Tua^2) (16).

Data analysis

First, True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) values were calculated using the sensitivity and specificity of the studies, and miRNAs that were the same in at least 3 different articles were included in the meta-analysis process.

Forest plots and combined sensitivity and specificity analysis with 95% confidence intervals (CIs) were drawn. Low, moderate, and high diagnostic performances were considered using AUC values of 0.5–0.7, 0.7–0.9, and 0.9–1.0, respectively. specificity, sensitivity, negative likelihood ratio, positive likelihood ratio, and diagnostic odds ratio were analyzed statistically (17, 18).

The clinical significance of circulating miRNAs in the diagnosis of CRC was assessed using Fagan's nomogram analysis, which is suitable for calculating and interpreting the results of diagnostic tests (19).

In addition, Deek funnel plots were generated to assess publication bias. The included studies were heterogeneous, so a random-effects model was used to report summary measures (20).

Subgroup analysis was performed based on the expression levels of circulating miRNAs (up-regulated or down-regulated). Stata 11 software (Stata Corp, College Station, TX, USA) and Review Manager [RevMan] Version 5.3 were used for data analysis.

Results

Characteristics of selected literatures

Initially, 1,207 articles were identified, of which 392, 393, and 422 were linked to PubMed, WoS, and Scopus, respectively. After removing duplicates and irrelevant articles by ENDNOTE, 541 articles remained. The titles and abstracts of all articles were read separately by two researchers, and the 291 excluded articles are detailed in Figure 1.

Finally, 250 articles were eligible, and their full texts were read by two researchers (AK and MMT), but 25 articles were again excluded because the full texts of the articles were not available and unfortunately, correspondence with the authors of these articles was unsuccessful. After all these steps, 225 articles remained, and after a full reading and removal of articles without mentioning AUC, sensitivity, and specificity, 126 articles remained as final articles (Figure 1).

The greatest number of studies related to China with 106, followed by Egypt and Iran with 21 and 10 articles in this field, respectively.

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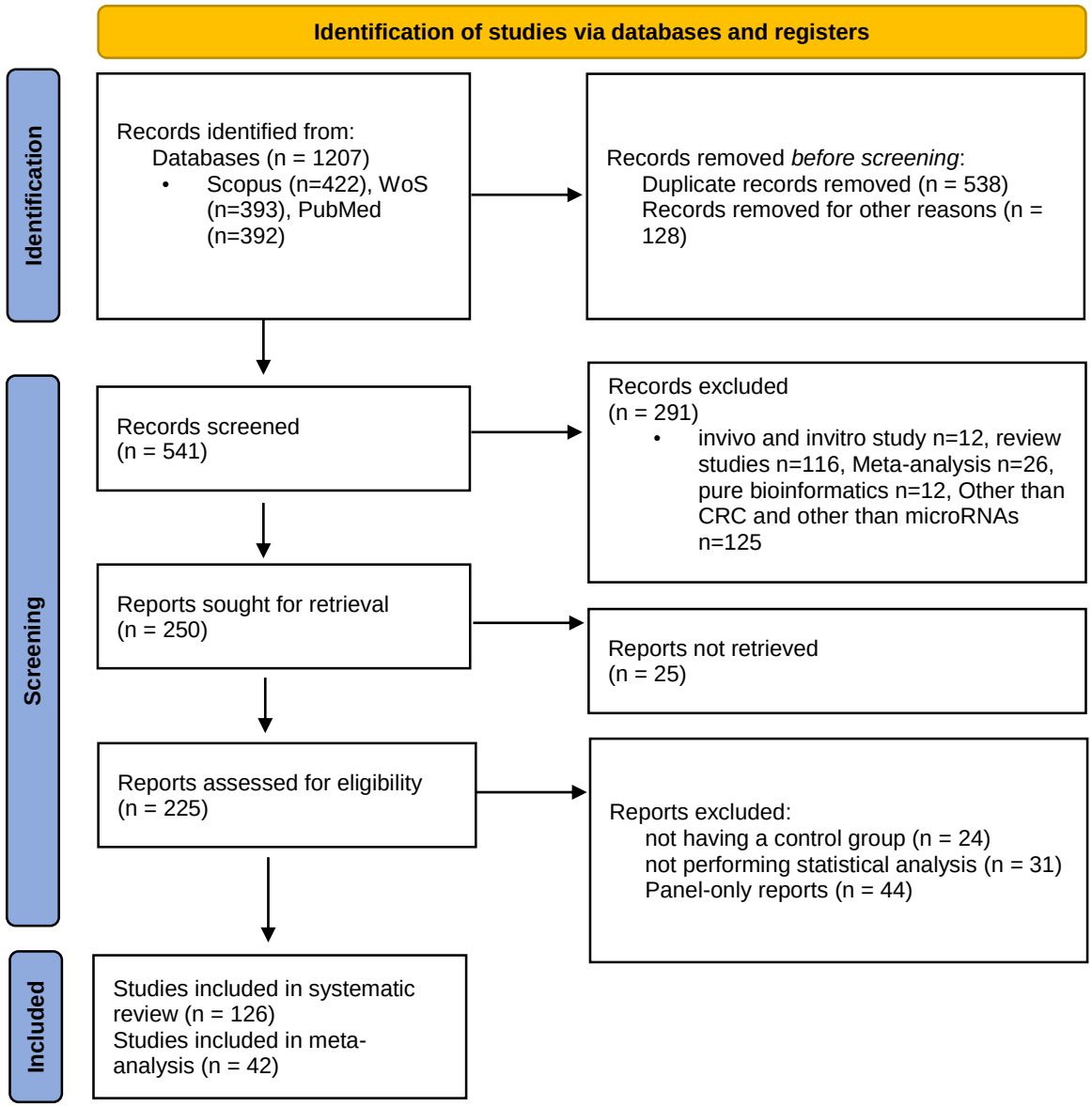

Figure 1. PRISMA 2020 flow chart of systematic review progress and study identification.

The sample size of the subjects studied (controls and CRC combined) ranged from 20 to 1182. The features of the selective case-control studies, including author and publication date, investigated miRNA(s), sensitivity (95% CI), specificity (95% CI), AUC, biological samples and, etc. were shown in Supplementary Table 3

Meta-analysis

Given the repetition of the same specific miRNAs in different articles, the researchers concluded that the studied miRNAs could have functioned as precious biomarkers for CRC detection. Therefore, articles that investigated a single miRNA (without a panel) in patients diagnosed with CRC compared to controls and reported the AUC and sensitivity and specificity of the corresponding miRNA were used for the meta-analysis. Finally, 6 specific miRNAs were identified in 42 studies and forest plots were drawn to evaluate the diagnostic accuracy of these miRNAs in CRC, and statistical analysis was carried out to obtain the pooled AUC, sensitivity (95% CI), and specificity (95% CI) for each miRNA, which can be seen in Figure 2 and Table 1.

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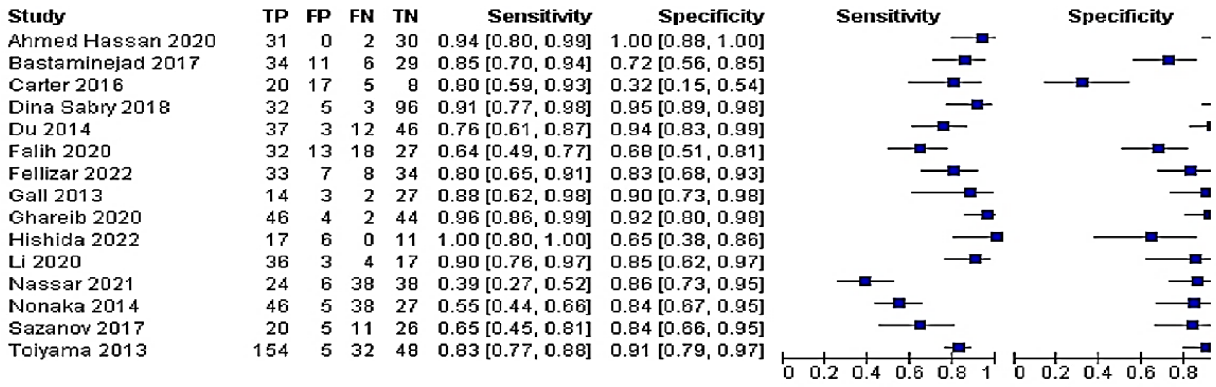
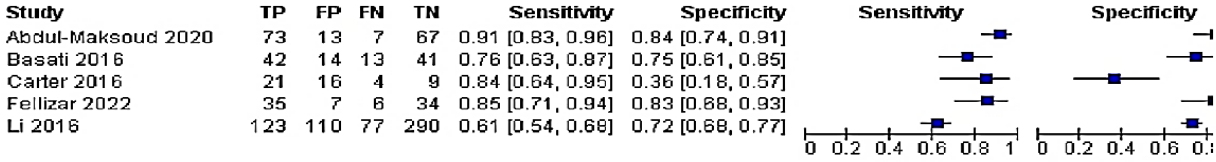
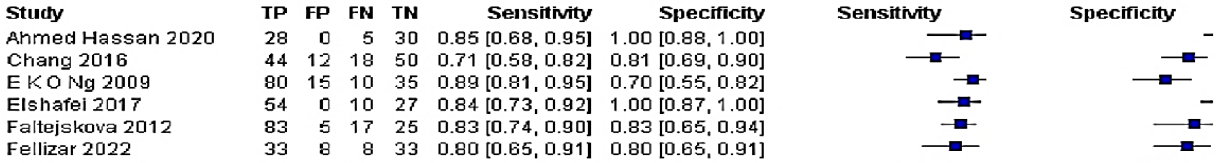


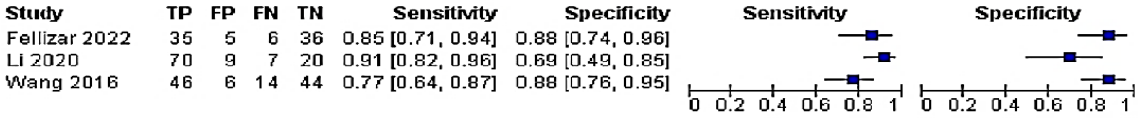
A. miR-21



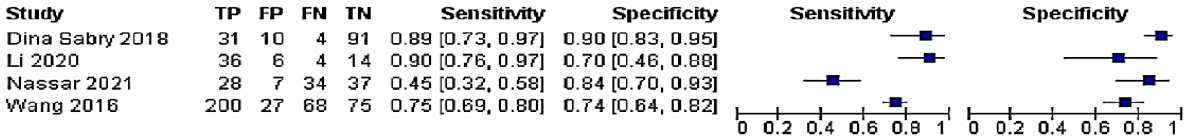
B. miR-29



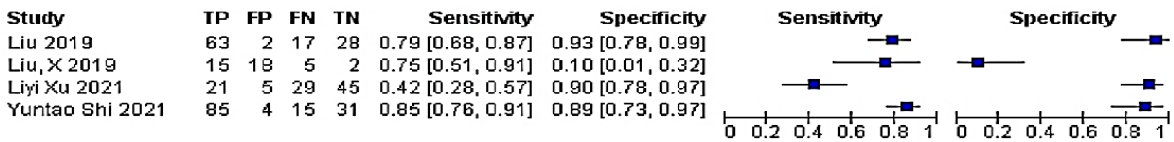
C. miR-92



D. miR-135



E. miR-210



F. miR-1290

Figure 2. Forest plots for studies on selected miRNAs in the present meta-analysis, including their sensitivity and specificity. A. miR-21, B. miR-29, C. miR-92, D. miR-135, E. miR-210 and F. miR-1290.

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Table 1. AUC, specificity and sensitivity of miRNAs included in meta-analysis, calculated by pooling studies using statistical analysis.

miRNA	Expression	AUC	Sensitivity	Specificity	sample	I^2 (%)	Study
miR-21	Upregulated	0.92	0.84	0.86	Plasma	85.58	(21-37)
miR-29	Upregulated	0.86	0.83	0.75	Plasma	88.89	(23, 36, 38)
	Downregulated	0.86	0.83	0.83	Plasma	92.57	(39-41)
miR-92	Upregulated	0.86	0.81	0.89	plasma	64.73	(36, 42-49)
miR-135	Upregulated	0.87	0.81	0.79	plasma	75.52	(37, 50-52)
	Downregulated	0.83	0.89	0.86	plasma	86.52	(36)
miR-210	Upregulated	0.86	0.77	0.81	plasma	54.95	(28, 29, 32, 53)
miR-1290	Upregulated	0.79	0.73	0.78	plasma	94.95	(54-56)

The results of the heterogeneity test across studies were also shown (I^2). The corresponding SROC curves were also plotted to assess the diagnostic accuracy of the miRNAs, which indicates the conceivable of miRNAs as non-invasive biomarkers for early diagnosis of CRC (Figure 3).

According to Figure 3 and Table 1, it was found that miR-21 (Figure 3A) may be a valuable molecular marker for CRC because the diagnostic value of miR-21 including AUC: 0.92, sensitivity: 0.84, specificity: 0.86. The diagnostic significance of other miRNAs can be seen in Table 1.

An additional factor that affects diagnostic accuracy is publication bias. A Deek's funnel plot was generated using Stata for miR-21, and it was observed that studies with it were equally spread on both sides of the regression line (P = 0.99), indicating no meaningful publication bias (Figure 4).

Fagan's nomogram analysis for miR-21 and miR-92 showed good results and it was found that people with a 20% chance of having CRC in the pre-test, when miR-21 is positive, the probability of cancer is 60% and the positive likelihood ratio is 6. When miR-21 was negative, the post-test probability decreased to 5% and the negative likelihood ratio is 0.19 (Figure 5A). Also, regarding miR-92, it was found that people who have a 20% chance of having CRC in the pre-test, when miR-92 is positive, the probability of cancer is 64% and the positive likelihood ratio is 7. While miR-92 was negative, the post-test probability decreased to 5% and the negative likelihood ratio is 0.21 (Figure 5B).

Results for other miRNAs showed that when the probability of colorectal cancer was 20% at pretest, the probability of cancer when miR-29 was positive was 46% (Figure 5C), in miR-135 49% (Figure 5D), in miR-210 51% (Figure 5E) and in miR-1290 45% (Figure 5F).

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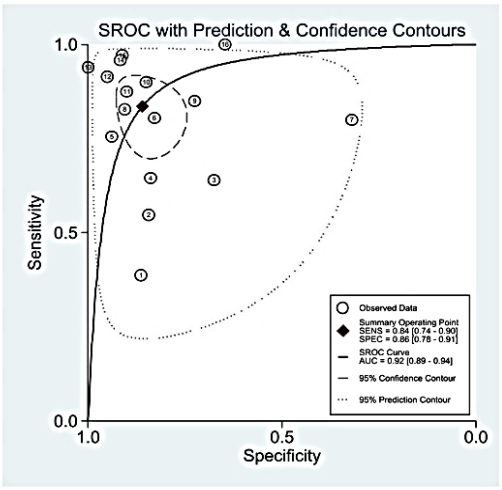
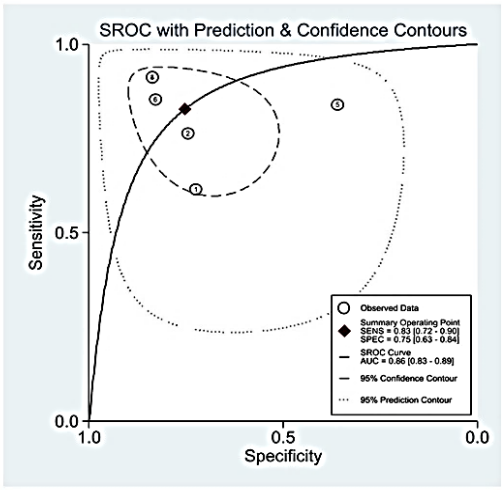
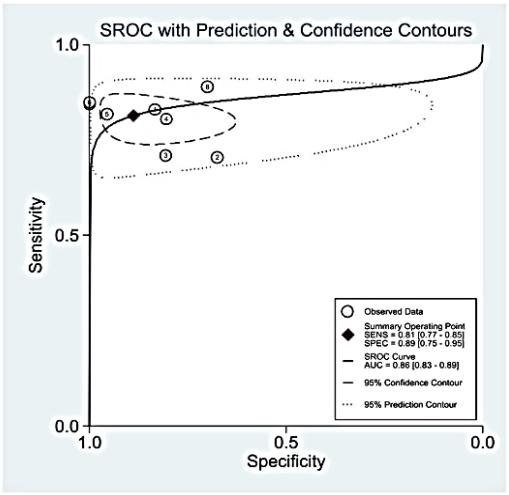


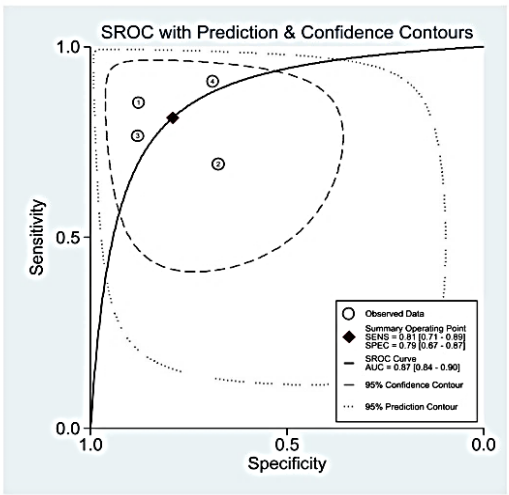
A. miR-21



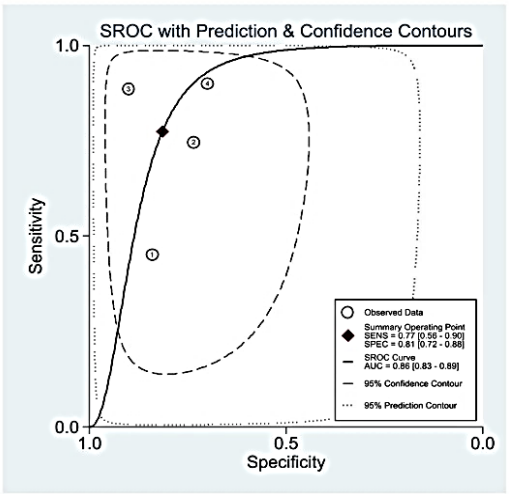
B. miR-29



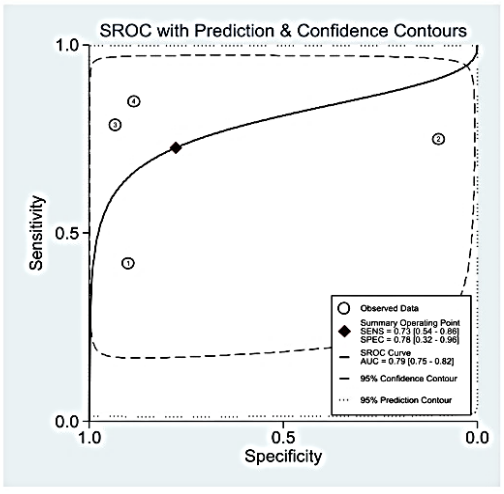
C. miR-92



D. miR-135



E. miR-210



F. miR-1290

Figure 3. SROC of circulating miRNAs in the diagnosis of CRC. A. miR-21, B. miR-29, C. miR-92, D. miR-135, E. miR-210 and F. miR-1290.

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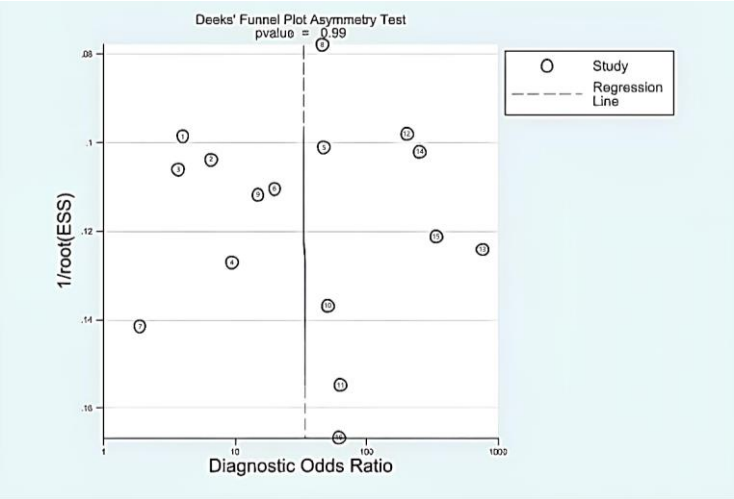

Figure 4. Deek's funnel diagram for assessing potential bias for miR-21.

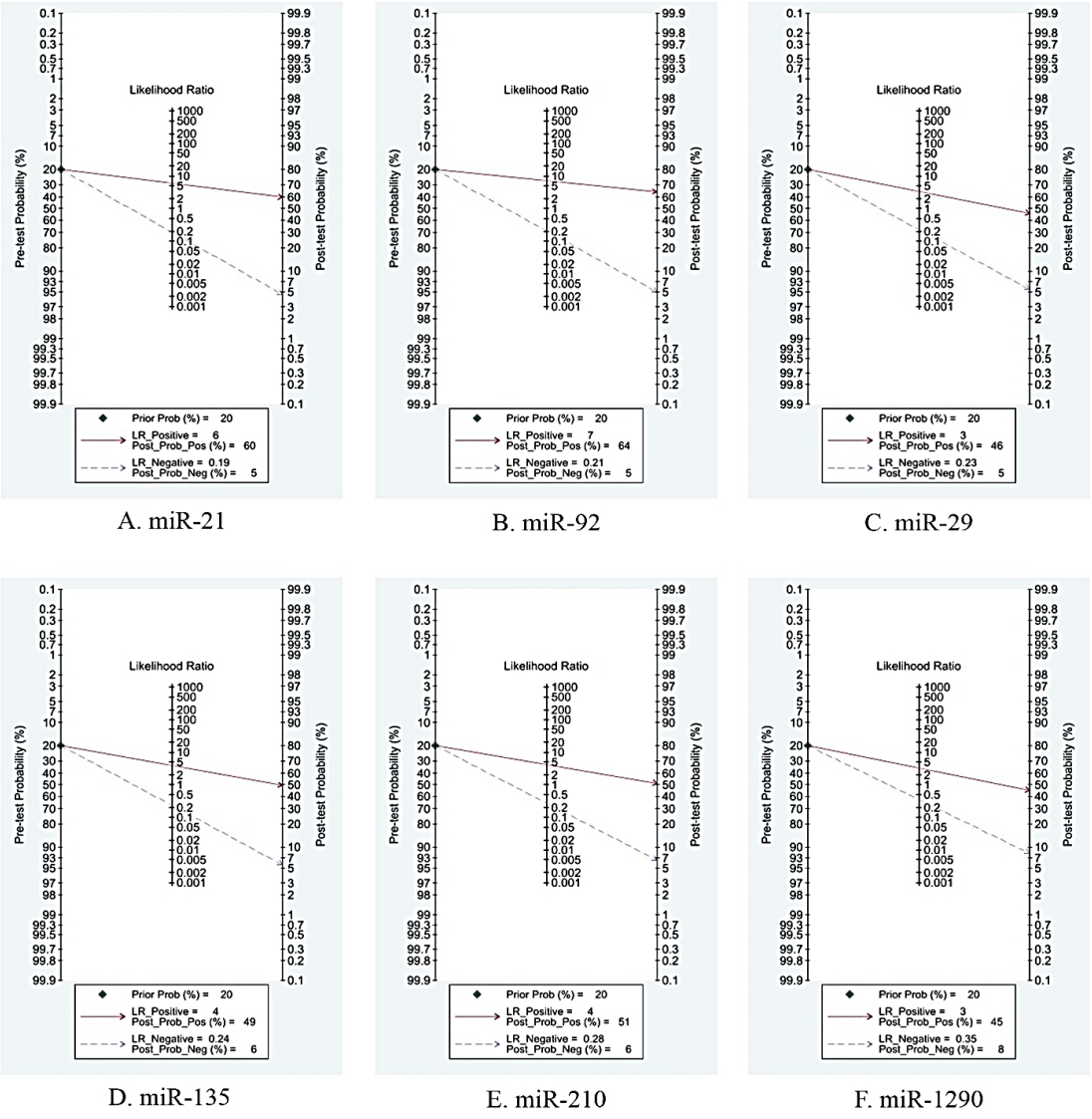

Figure 5. Fagan nomogram diagram with 20% probability of disease before testing. A. miR-21, B. miR-92, C. miR-29, D. miR-135, E. miR-210 and F. miR-1290.

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Discussion

MiRNAs are small, non-coding RNAs that are transcribed as primary miRNAs (pri-miRNAs). Mature double-stranded miRNAs, approximately 22 nucleotides, is the result of further processing by the Drosha and Dicer enzymes in the nucleus and cytoplasm, respectively.(17).

Mature miRNAs, which are actively released from cells, are durable in extracellular fluid such as plasma, serum, saliva, urine, and feces, and can be used to diagnose diseases such as cancer (57, 58).

MiRNAs play two essential roles in cancer as tumor suppressors and oncogenes. Overexpression of miRNAs acts as oncogenes and enhances oncogenic processes by regulating tumor suppressors or other genes participated in cell differentiation. Conversely, down regulation of miRNAs that act as tumor suppressors leads to increased expression of specific proteins with oncogenic qualities (17).

Previous researches have indicated that miRNA expression is dysregulated in cancers of the esophagus, lung, liver, pancreas, bladder, ovary, and stomach (59). In this survey, 123 published studies containing 241 body fluid-based deregulated miRNAs for CRC diagnosis were reviewed. It is hypothesized that excess expression of particular miRNAs, known as oncogenes, in the presence of disease is due to cancer. Also, down regulated markers should not necessarily be evaluated as trustworthy biomarkers for CRC diagnosis, but can be used as a reliable predictive significance for different levels of that miRNA without the disease (17).

The discovery of tumor-associated miRNAs in plasma has sparked many studies and significant advances in this field. However, colonoscopy is still the gold standard screening test for CRC and liquid-based miRNAs could provide a new, more convenient platform for CRC diagnosis (60, 61). To assess the diagnostic importance of liquid-based miRNAs, data from 42 eligible studies were subject matter of meta-analysis. The studies were not restricted to a specific geographical region, as shown in Supplementary Table 3, and the sample type in all studies, plasma, was found to be a reliable sample, and the miRNA quantification method in all studies was qRT-PCR (real-time reverse transcription-PCR), which is a suitable method for assessing miRNA levels. The diagnostic power of our studied miRNAs was compared with conventional serum tumor biomarkers for the CRC diagnosis, including cancer antigen (CA) 19-9, carcinoembryonic antigen (CEA), CA242, and CA125. These values were extracted from the study by Lu et al., who investigated the mentioned markers among 358 CRC patients and 298 healthy individuals and showed that the AUC, Sensitivity, and Specificity values were 0.682, 37.71, and 90.60 for CEA, 0.560, 34.92, and 78.19 for CA19-9, 0.590, 25.14, and 88.93 for CA125, and 0.651, 66.20, and 59.73 for CA242, respectively (62). Our survey showed that plasma-based miRNAs have high detection accuracy for CRC diagnosis.

miR-21 is an oncogenic miRNA that modulates the expression of specific genes such as programmed cell death 4. In our research, 17 different studies were identified, which in total showed that miR-21 was upregulated in 757 CRC patients compared to 601 healthy individuals. Bastaminejad et al. (2016) declared miR-21 as a potential diagnostic biomarker. This article evaluated the expression of miR-21 in 40 patients diagnosed with CRC and 40 healthy people. MiR-21 expression levels are up-regulated 12.1 times more compared to the serum of healthy people. In serum testing, miR-21 can discriminate CRC patients from controls with an AUC of 0.783, a sensitivity of 86.05%, and a specificity of 81.08% (35). miR-21 has shown excellent results in various studies and in our study, it distinguished healthy individuals from CRC individuals with an AUC of 0.92, sensitivity of 84% and specificity of 86%, which is in the high range in terms of diagnostic accuracy and is better than other serum tumor biomarkers for CRC diagnosis, including CEA, CA19-9, CA125 and CA242. CEA is the best serum tumor biomarker and is commonly used, with an AUC of 0.682, sensitivity of 37.71% and specificity of 90.60%, and these values indicate the high diagnostic power of miR-21.

miR-29 is another miRNA that has been reported to be deregulated in 6 studies with 401 CRC patients and 601 healthy individuals, three papers reported that this miRNA was downregulated (Abdul- Maksoud et al. 2021, Li et al. 2016, Basati et al. 2016) while three papers reported an upregulation of this miRNA in CRC patients compared to healthy subjects (Carter et al. 2016, Rapado-González et el. 2019, Fellizar et al. 2022).

Previous articles have demonstrated that members of the miR-29 family play roles as tumor suppressors in some cancers such as hematopoietic, cholangiocytic,

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and lung tumors, but some recent studies have shown mixed results. Consequently, miR-29 can act as either an oncogene or a tumor suppressor gene, based on the context (36, 39, 63). The power of this miRNA to discriminate between healthy individuals and CRC subjects in our study was much better than other conventional serum tumor biomarkers for CRC diagnosis (AUC= 0.86, sensitivity = 83%, and specificity =75%). Interestingly, when examined as a negative regulator, its specificity only increased to 83%.

Another miRNA that is a candidate biomarker for diagnosis is miR-92. Eight different papers reported regulation of this miRNA in 582 CRC patients compared to 348 healthy controls. In our study, miR-92 distinguish CRC patients from controls with an AUC of 0.86, sensitivity of 81%, and specificity of 89%, which is a very good result for a noninvasive biomarker and performs much better than other common serum tumor biomarkers for CRC diagnosis, but studies have shown that it is not specific for CRC alone (46).

The results of miR-135, which was examined in a total of 178 CRC patients and 120 healthy individuals, are also controversial. In our review, 3 papers reported up regulation of miR-135(Wang et al., Islamizadeh et al., Gall et al.). Allan Fellizar et al. reported down regulation of this miRNA. This family has the potential to be tumor suppressors and oncogenes (36, 37, 50, 52). In our study, this miRNA distinguished healthy subjects from CRC subjects with an AUC of 0.87, sensitivity of 81%, and specificity of 79%, indicating its high diagnostic power compared to other conventional serum tumor biomarkers for CRC diagnosis.

Up regulation of miR-210 in cancer patients may be useful as an inducer of apoptosis in CRC cells because it is a key mediator in ROS production and causes cell proliferation to decrease and block them in the G2/M phase of the cell cycle. It has also been illustrated that excess expression of miR-210 is company with poor prognosis in these patients. Increased expression of miR-210 is mainly regulated by HIF transcription factors and hypoxia is contributed with poor prognosis of cancer patients (64).

MiR-210 was investigated in four papers with 405 patients diagnosed with CRC and 267 healthy subjects for early detection of CRC, in all of which, it was associated with increased expression and distinguished healthy subjects from CRC subjects with an AUC of 0.86, sensitivity of 77%, and specificity. 81%, indicating that this biomarker is a good candidate for CRC diagnosis and is better than other serum tumor biomarkers for CRC diagnosis, including CEA, CA19-9, CA125, and CA242.

Finally, circulating miR-1290 was identified as an effective biomarker for detection and monitoring of CRC in early steps. In our study, this miRNA discriminated 135 healthy individuals from 250 CRC patients with an AUC of 0.79, sensitivity of 73%, and specificity of 78%. Over expression of miR-1290 is significantly associated with disease progression because it has a tumor-promoting effect and is involved in the occurrence and development of CRC (56).

According to the results of this study on miRNAs and its comparison with previous studies, potential biomarkers that are effectively used in clinical trials, such as fecal hemoglobin, CEA, CA19-9, CA125, and CA242, are not very promising diagnostic targets for personalized medicine. Therefore, specific genetic biomarkers are essential for individualized and optimal diagnosis and treatment (28, 62).

Our results also showed that the diagnostic accuracy of miRNAs found in plasma outperformed fecal-based miRNAs for CRC, as the pooled AUC value for separating healthy subjects and CRC patients was 0.811. The pooled studies of miRNAs in identifying CRC from healthy subjects illustrated a sensitivity of 58.8% (95% CI: 51.7–65.5%) and a specificity of 84.8% (95% CI: 81.1–87.8%), indicating that the miRNAs found in the present study showed better results (65).

In the present study, a large number of studies investigated plasma or serum miRNAs in CRC patients, we found that some miRNAs were significantly deregulated in the reviewed studies and could serve as biomarkers, but in the meta-analysis, it was found that some miRNAs have good diagnostic performance and could serve as promising clinical markers for CRC diagnosis in the future (Table 1). These miRNAs were similarly replicated in a significant number of studies, increasing their diagnostic value. For example, miR-21 was investigated in 17 studies and showed that it increased in a total of 757 CRC patients compared to 601 healthy subjects. Our study performed a literature search in 3 different databases, which resulted in a significant scale of studies and a large number of participants. The

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other strengths of this study were no publication bias and excellent methodological quality of the studies, which lowered the risk of bias. All the studies reviewed used the same measurement methods for miRNAs, which ensured and made the comparison of results between different studies more reliable. Some limitations of the present study were the severe heterogeneity in the number of subjects studied and the presence of diverse miRNA panels in the included studies, which made it challenging to obtain the diagnostic value of individual miRNAs and to compare the results between studies. However, despite the limitations of CRC diagnosis, evaluation of miRNA expression combined with other clinical and diagnostic tests and comprehensive analysis, is a promising strategy for CRC diagnosis.

Future directions and limitations

The expression of miRNAs changes dynamically and rapidly in response to internal or external stimuli, making them suitable for real-time and dynamic monitoring during tumor growth, from initiation to progression and even recurrence (66). Dysregulated expression levels of miRNAs have been associated with prognosis in AML and are used in the clinic. Overexpression of miR-155 and miR-3151 predicts an unfavorable outcome in CN-AML, whereas overexpression of miR-181a predicts a favorable outcome in both CN-AML and cytogenetically abnormal AML (67). There are good examples of their potential role in diagnosis and prognosis in CRC, for example, increased miR-21 is associated with poor overall survival and cancer-free survival in patients and as a marker for lymphatic metastasis, miR-29 as a biomarker for early diagnosis and miR-34a as a biomarker for predicting patient recurrence (68). These findings demonstrate the potential of circulating miRNAs for assessing tumor stage and progression (69). There are also examples of successful therapies, such as miravirsen, an inhibitor of miR-122, or cobomarsen, an inhibitor of miR-155, which have shown good results in clinical trials (70).

The distinct roles and molecular effects of miRNAs in cancer highlight their challenges in clinical settings, and complicate clinical outcomes for miRNA-based applications (71).

Circulating miRNAs can be obtained quickly and without severe damage, but the influence of blood cell miRNAs (present in red blood cells, leukocytes, and platelets) should not be overlooked. Therefore, it is impossible to consider whole blood as a biological fluid for the detection of circulating miRNAs, and plasma/serum should be used, taking into account appropriate preparation techniques (69).

A very important challenge is the variability in miRNA expression, which significantly affects miRNA-driven processes. miRNAs with consistent expression profiles in certain cancers are suitable targets for diagnosis and therapy, such as let-7 (as a tumor suppressor miRNA) (72). Therefore, understanding and addressing the variability in miRNA expression, as demonstrated by The Cancer Genome Atlas (TCGA) data, is crucial for their appropriate use.

miRNAs are very stable in the bloodstream and their levels will not change after repeated freeze/thaw cycles; however, it is recommended to avoid excessive freeze/thaw (69).

Finally, a large number of potentially useful miRNA biomarkers have been shown to be unaltered in normal humans, so personalized approaches could revolutionize the application of miRNAs. These strategies exploit the complex interactions between miRNAs, mRNAs, and lncRNAs with the aim of tailoring therapy and diagnosis to the unique molecular profiles of patients (73).

In our meta-analysis, miR-21, miR-29, miR-92, miR-135, miR-210 and miR-1290 had good diagnostic value for CRC, and outperformed conventionally used serum tumor biomarkers in the clinic, such as CEA, CA19-9, CA125, and CA242. Potentially, miRNAs might be utilized as an inexpensive, non-invasive and blood-based marker for CRC diagnosis in the clinic in the future. Nevertheless, large-scale and high-quality clinical trials are required to be accompanied to confirm our findings.

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