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REVIEW

Diagnostic Performance of Circulating miRNA-92a and Related Circulating miRNA Panels for Colorectal Cancer: An Updated Systematic Review and Meta-Analysis

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Background: Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide and the third most frequently diagnosed malignancy. Circulating microRNAs, particularly miRNA-92a, have gained prominence as non-invasive biomarkers due to their stability in biological fluids and disease-specific expression patterns.

Objective: This study evaluates the diagnostic performance of circulating miRNA-92a for non-invasive colorectal cancer detection, both as an individual biomarker and in combination with other circulating miRNAs, including markers that are either members of the miRNA-92a family or unrelated miRNA candidates.

Methods: This review was registered in PROSPERO (CRD420251070402). A systematic search of PubMed, ScienceDirect, and Google Scholar was conducted for articles published up to May 2025 in accordance with PRISMA guidelines. Eligible articles evaluated circulating miRNA92a for CRC diagnosis, used appropriate reference standards, and reported extractable sensitivity and specificity data. A bivariate random-effects model in STATA/BE v18.0 was used to generate pooled estimates of sensitivity, specificity, PLR, NLR, logDOR, and AUC. Study quality was assessed using QUADAS-2, and publication bias was examined with Deeks' funnel plot asymmetry test.

Results: Twenty-two studies from sixteen articles, involving 1918 CRC patients and 1446 healthy controls, were included. Circulating miRNA-92a and miRNA-92a–related circulating panels demonstrated pooled sensitivity and specificity of 86% and 91%. Overall diagnostic performance was high, with an AUC of 0.87. The logDOR was 3.71, with a pooled PLR of 18.54 and an NLR of 0.38. Subgroup analyses showed comparable accuracy between singlemarker and panel-based assays, and serum samples yielded more consistent results. QUADAS-2 indicated acceptable methodological quality, and no significant publication bias was detected ($p = 0.06$).

Conclusion: Circulating miRNA-92a demonstrates superior diagnostic performance and considerable potential as a non-invasive biomarker for early CRC detection. Further large-scale prospective studies are required to standardize testing protocols and confirm their clinical applicability.

Keywords: colorectal cancer, diagnostic accuracy, meta-analysis, miRNA-92a, noninvasive biomarker

Introduction

Colorectal cancer (CRC) is still one of the most often diagnosed cancers worldwide and is now a leading cause of cancer-related death. Specifically, CRC ranks second in cancer-related mortalities, with roughly 900,000 deaths, and third in

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global incidence, with about 2 million new cases.[1] The high prevalence and mortality rates associated with CRC have translated into a substantial economic burden on healthcare systems, amounting to billions of dollars in expenditures globally.[2] These figures highlight that CRC is not only a significant clinical challenge but also poses far reaching impacts on economic and societal sectors.

Although early-stage CRC typically responds well to treatment, current diagnostic strategies remain inadequate for timely detection. Colonoscopy followed by histopathological biopsy remains the diagnostic gold standard. However, its invasiveness and high cost prevent it from being widely used. Additional diagnostic options have also been studied, such as molecular markers like carcinoembryonic antigen (CEA), fecal occult blood testing (FOBT), and computed tomography (CT) imaging.[3] Nevertheless, these methods are hindered by suboptimal sensitivity and specificity, along with broad detection thresholds that compromise their reliability in early-stage diagnosis.[4,5] Therefore, there is a need for novel, non-invasive biomarkers with improved diagnostic accuracy for the early diagnosis of CRC.

MicroRNAs (miRNAs) have become a viable option for non-invasive biomarkers in recent years, especially for CRC early detection. These short, noncoding RNA sequences, which range in length from 18 to 25 nucleotides, are involved in several essential cellular functions, including differentiation, apoptosis, metastasis, and proliferation.[6] Notably, miRNAs exhibit remarkable stability in various biological fluids and demonstrate resistance to enzymatic degradation, fluctuations in pH, and multiple freeze thaw cycles, making them highly suitable for clinical diagnostic applications.[7,8] Furthermore, significant variations in miRNA expression between normal and malignant have been documented, confirming their value as extremely sensitive and precise biomarkers for the identification of cancer.[8]

Among these, miRNA-92a family, comprising a group of highly conserved microRNAs including miR-25, miR-92a-1, miR-92a-2, and miR-363, has emerged as one of the most extensively investigated biomarker candidates in colorectal cancer research.[9] Several studies have reported that its upregulation correlates with tumorigenesis, progression, and metastasis, while also demonstrating a capacity to discriminate CRC from healthy patients. Despite its clinical promise, however, inconsistencies across studies in terms of diagnostic accuracy and population heterogeneity have limited its routine application in practice.[10]

A previous meta-analysis published in 2019 provided important insights into the potential utility of miRNA-92a and related panels for CRC diagnosis and recurrence prediction.[11] However, in the years since, a substantial number of new studies have been published, incorporating improved methodologies, diverse sample populations, and larger datasets. Thus, an updated systematic review and meta-analysis are needed to reassess the diagnostic performance of miRNA-92a, lower inter-study variability through improved statistical synthesis, and offer more substantial evidence in favor of its inclusion in CRC screening methods.

Methods

Eligibility Criteria and PICOS Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was followed in conducting this systematic review and meta-analysis.[12] The protocol has been registered with Prospero with the number CRD420251070402. The eligibility criteria were defined using the PICOS framework, as outlined in Table 1. Articles were included if: (1) investigated miRNA-92a in human subjects; (2) used an observational design appropriate for diagnostic accuracy assessment (eg, case–control, cross-sectional, or cohort studies); and (3) explicitly identified the condition as colorectal cancer or colorectal carcinoma within the title or abstract. Exclusion criteria comprised: (1) articles not published in English; (3) articles with irrelevant designs. (eg, reviews, case reports); and (4) papers with incomplete or non-extractable data.

Information Sources

Using predetermined inclusion and exclusion criteria, two independent reviewers RH and SA screened full-text articles, abstracts, and titles from the PubMed, Google Scholar, and ScienceDirect databases to find relevant studies. In addition, a snowballing approach was employed on May 10, 2025, to enhance the comprehensiveness of the search.

Table 1 PICOS Framework

PICOS	Description
Participants	Individuals with CRC and non-CRC participants, including both patients without CRC and healthy controls.
Intervention	Single miRNA-92a analysis or miRNA-92a–related circulating panels
Comparison	Histopathological confirmation of CRC, with colonoscopy used as the diagnostic procedure guiding tissue sampling.
Outcome	Diagnostic accuracy parameters, including sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), log diagnostic odds ratio (DOR), and the area under the receiver operating characteristic (ROC) curve (AUC).
Study design	Case–control and cohort studies

Search Strategy

A literature search was conducted by searching for studies published until May 10, 2025, with the following keywords:

1. Search: ("microRNA-92a" OR "miRNA-92a" OR "miR-92a")
2. Search: ("Colorectal cancer" OR "CRC")
3. Search: ("Diagnosis" OR "Diagnostic")
4. Search: ("Specificity" OR "Sensitivity")
5. Search: ("Serum" OR "Plasma" OR "Blood" OR "Circulating")
6. Search #1 AND #2 AND #3 AND #4 AND #5

Selection Process

Two separate investigators RH and SA thoroughly reviewed the titles and abstracts as part of the selection process. Discussions were held to settle disagreements until a consensus was reached. Next, the researchers independently screened each retrieved article in pairs. In cases of disagreement during the study selection process, an independent third-party expert was consulted to provide an impartial evaluation and help resolve any disputes between the authors.

Data Collection Process and Data Items

Investigators RH and SA conducted data extraction from the included articles independently. Disagreements were solved by fully discussing with the third senior investigator (IP) to reach a consensus. The data extraction form was designed based on previous studies.[13,14] After comparing the extracted data, any differences were discussed and settled. Before data analysis, the accuracy of the data was verified and double-checked before being entered into STATA/BE (v.18.0) statistical software. The extracted data includes: (1) first author; (2) publication year; (3) country; (4) miRNA; (6) number of case and control participants; (7) sensitivity; (8) specificity.

Study Risk of Bias Assessment

To evaluate the quality of the included articles, two independent reviewers RH and SA used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) instrument. The evaluation encompassed four primary areas: reference standard, flow and timing, index test, and patient selection. The Review Manager (RevMan) software version 5.3 was used to carry out this assessment. As a result, the appraisal outputs classified the applicability and bias risks as unclear, low, or high. Disagreements regarding bias risk assessments and the justifications for these assessments were resolved through discussion until the two investigators reached an agreement. In cases of disagreement during the risk of bias assessment, an independent third-party expert was consulted to provide an impartial evaluation and help resolve any disputes between the investigators.

Effect Measures and Synthesis Methods

STATA/BE version 18.0 was used to conduct the diagnostic meta-analysis (StataCorp, College Station, TX, USA). Pooled diagnostic performance estimates, such as sensitivity, specificity, PLR, NLR, logDOR, and AUC, along with their

corresponding 95% CIs, were computed using a random-effects bivariate model. Along with additional pertinent information from the papers, the primary data points (true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN)) were either taken straight from the included studies or computed based on sensitivity and specificity. In addition to a summary receiver operating characteristic (SROC) curve, forest plots for sensitivity and specificity were made to graphically represent the diagnostic performance of miRNA-92a and its associated biomarkers. The AUC served as a global measure to assess the overall discriminative ability of the biomarkers tested.[13,14]

Statistical heterogeneity was evaluated using Cochran's Q test (with significance set at $p < 0.05$) and Higgins's I^2 statistic, which quantifies the proportion of total variability attributed to heterogeneity. An I^2 value $\geq 50\%$ and a p-value ≤ 0.05 were indicative of significant heterogeneity. In cases of substantial heterogeneity, potential sources were explored through subgroup analyses to assess the robustness of the findings. Publication bias was evaluated using Deeks' funnel plot asymmetry test, with a p-value greater than 0.05 suggesting minimal bias. Furthermore, Fagan's nomogram was employed to estimate the post-test probability and clinical applicability of miRNA-92a as a diagnostic biomarker for colorectal cancer and related conditions.[14]

Results

Study Selection and Characteristics

A total of 22 studies derived from 16 articles met the inclusion criteria, including 1918 patients with confirmed colorectal cancer (CRC) and 1446 healthy controls matched for age and sex (Figure 1). These studies were conducted across various geographic regions, with the majority originating from China (n = 9) and Egypt (n = 5), along with contributions from Germany (n = 1), Morocco (n = 1), and the Philippines (n = 1). All studies were published between 2012 and 2025,

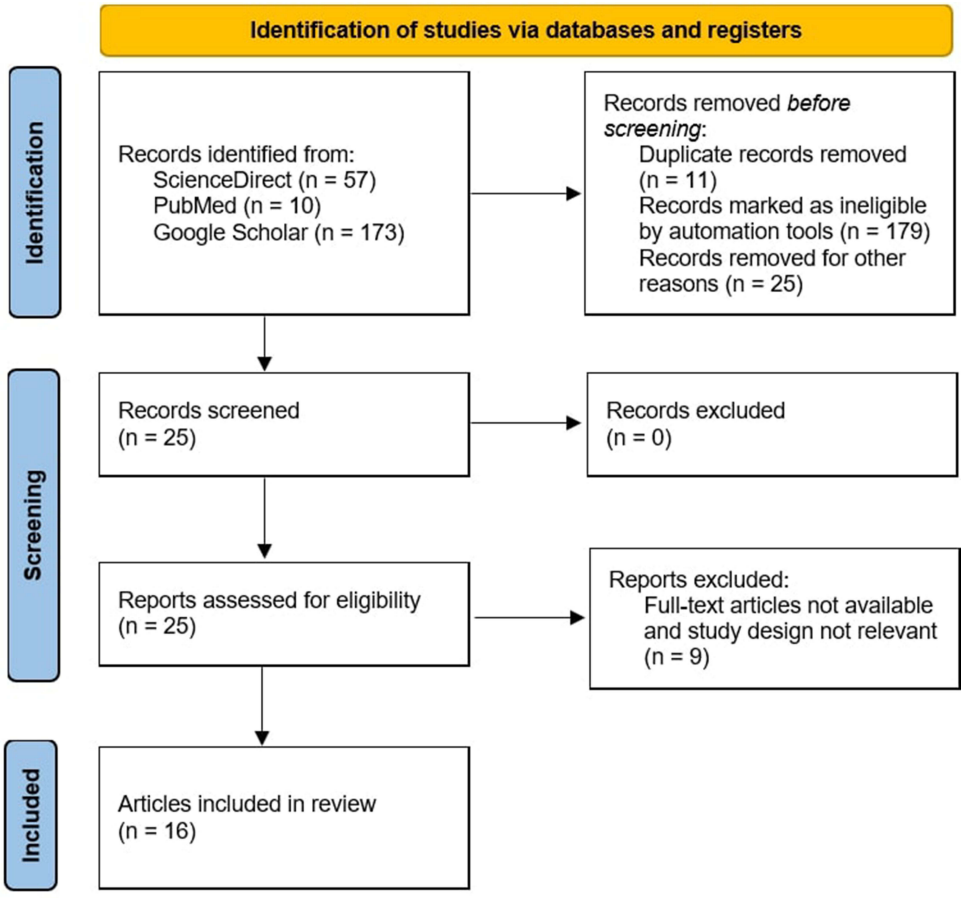

Figure 1 PRISMA flow diagram of study selection.

indicating a growing interest in exploring the diagnostic potential of miRNA-92a and its combinations in recent years. The specimens analyzed were primarily serum (16 studies) and followed by plasma (6 studies). Sample sizes varied widely, ranging from smaller studies (eg, Fu et al, 2018, with 28 participants) to larger case–control studies (eg, Chang et al, 2016, with 398 participants). Specificity ranged from 68% to 100% and reported sensitivity values ranged from 66% to 98%. The main features of all the included studies are listed in Table 2.[15–31]

Risk of Bias (QUADAS-2)

According to the QUADAS-2 assessment of the 16 included articles (Table 3), no study exhibited a high risk of bias in the patient selection domain; most were rated low risk, with a few classified as unclear due to limited sampling information. In the index test domain, several articles showed unclear risk because prespecified thresholds or blinding procedures were not reported, while the remainder were deemed low risk. No high-risk ratings were observed. Most articles demonstrated low risk in the reference standard domain, reflecting the use of established criteria such as colonoscopy or histopathology, whereas a small number were rated unclear due to insufficient detail on independent interpretation. For flow and timing, many of articles were assessed as low risk, with a minority rated unclear owing to incomplete reporting on the uniformity of reference testing or the interval between index and reference procedures.

Diagnostic Accuracy of miRNA-92a

The diagnostic performance of miRNA-92a and miRNA-92a-related circulating panels in CRC was assessed through an analysis of 22 eligible studies. This analysis revealed moderate heterogeneity in the sensitivity and specificity results, with an I^2 value of 52.79% ($p = 0.73$), indicating statistically insignificant variability across the studies. Consequently, a random-effects meta-analysis model was employed to appropriately pool the results. [14] The pooled sensitivity was 0.86 (95% CI: 0.81–0.90, $p < 0.001$) and specificity was 0.91 (95% CI: 0.86–0.94, $p < 0.001$), reflecting a high level of diagnostic accuracy (Figure 2). Additionally, the area under the summary receiver operating characteristic (SROC) curve (AUC) was 0.87 (95% CI: 0.84–0.90), suggesting high overall diagnostic performance of miRNA-92a and its combination biomarkers for CRC detection (Figure 3). The positive likelihood ratio (PLR) was 18.54 (95% CI: 13.76–23.31), and the negative likelihood ratio (NLR) was 0.38 (95% CI: 0.25–0.51) (Figure 4). The logDOR was 3.71 (95% CI: 3.19–4.23), indicating a high ability to distinguish between CRC cases and non-cases. Despite observed heterogeneity in several parameters (PLR: $I^2 = 99.9\%$, logDOR: $I^2 = 95.9\%$, AUC: $I^2 = 88.8\%$), these findings highlight the promising potential of miRNA-92a as a non-invasive biomarker for CRC diagnosis (Figure 5).

Subgroup Analysis

Subgroup analyses were conducted according to research size, sample type, country, and the miRNA-92a-related circulating panels (Table 4). Studies conducted in Egypt demonstrated higher pooled sensitivity (92%) and a comparable specificity (92%) compared to those from China (83% and 91%, respectively). The AUC also slightly favored the Egyptian subgroup (0.90 vs 0.87). Both subgroups demonstrated excellent positive likelihood ratios (PLR >20), indicating a strong rule-in potential. The negative likelihood ratio (NLR) was lower in the Egyptian subgroup (0.33 vs 0.41), suggesting better rule out capacity. However, despite these promising results, substantial heterogeneity persisted in the AUC, PLR, and DOR ($I^2 > 55\%$, $p < 0.05$), limiting the certainty of pooled accuracy estimates.

In terms of sample type, miRNA-92a measured in serum consistently outperformed plasma samples. Serum-based testing yielded higher sensitivity (89% vs 80%), better specificity (92% vs 83%), and stronger discriminative capacity (AUC: 0.89 vs 0.81). PLR values were also markedly higher in the serum subgroup (23.20 vs 7.84), indicating a greater ability to rule in disease. Nevertheless, PLR, AUC, and DOR parameters remained affected by significant heterogeneity.

A similar pattern was noted when comparing studies by sample size. Smaller studies ($n < 100$) appeared to report more favorable diagnostic outcomes, with higher sensitivity (93% vs 81%) and AUC (0.93 vs 0.84) compared to larger studies. Although these findings may suggest publication or reporting bias, heterogeneity remained unresolved in this subgroup, particularly for AUC, logDOR, and PLR, underscoring the need for caution in interpreting small-sample meta-estimates.

Table 2 Data Extraction Results from Included Studies

No	Author, Year	Country	miRNA	Sample Size (Case/Normal)	Specimen	Sensitivity	Specificity
1	Wang (2012)[15]	China	miR-29a, miR-92a and miR-760	90/58	Plasma	83%	93%
2	Liu (2013)[16]	China	miR-92a, miR-21	200/80	Serum	68%	91%
3	Luo (2013)[17]	Germany	miR-92a, miR- 18a, miR-20a, miR-21, miR-29a, miR-106b, miR133a, miR-143, miR-145, miR-342-3p, miR-532-3p, miR-181b	80/144	Plasma	72%	75%
4	Wang (2014)[18]	China	miR-92a, miR-21, let-7g, miR-31, miR-181b, miR-203	30/30	Serum	83%	97%
5	Wang (2014)[18]	China	miR-92a, miR-21, let-7g, miR-31, miR-181b, miR-203	83/59	Serum	96%	88%
6	Zheng (2014)[19]	China	miR-92a, miR-19a, miR-223, miR-422a	160/94	Serum	91%	89%
7	Zheng (2014)[19]	China	miR-92a, miR-19a, miR-223, miR-422a	117/102	Serum	84%	92%
8	Chang (2016)[20]	China	miR-92a, miR-223	215/183	Plasma	76%	71%
9	Liu (2018)[21]	China	miR-92a, miR-21, miR-29a, miR-125b	85/78	Serum	85%	99%
10	Fu (2018)[22]	China	miR-92a, miR-17	18/10	Serum	91%	83%
11	Fathi (2025)[23]	Morocco	miR-21, miR-29a and miR-92a	50/50	Plasma	82%	92%
12	Fathi (2025)[23]	Morocco	miR-92a	50/50	Plasma	74%	83%
13	Shi (2020)[24]	China	miR-92a-1	148/68	Serum	81.80%	95.60%
14	Hassan (2021)[25]	Egypt	miR-92a	52/20	Serum	94.23%	100%
15	Hassan (2021)[25]	Egypt	miR-21, miR-92a	52/20	Serum	96.15%	100%
16	Said (2017)[26]	Egypt	miR-21, miR-92a	35/15	Serum	97.10%	93.30%
17	Said (2017)[26]	Egypt	miR-92a	35/15	Serum	91.40%	80%

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18	Zaki (2022)[27]	Egypt	miR-92a	54/15	Serum	98%	94%
19	Elshafei (2017)[28]	Egypt	miR-92a	64/27	Serum	84.40%	84.40%
20	Fellizar (2022)[29]	Philippines	miR-92a-3p	36/36	Plasma	90%	88%
21	Elaguizy (2020)[30]	Egypt	miR-18a, miR-21, miR-92a	50/50	Serum	86%	90%
22	Elaguizy (2020)[30]	Egypt	miR-92a	50/50	Serum	66%	68%

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Table 3 The QUADAS-2 Assesses the Quality (Risk of Bias and Applicability Concern Evaluation) of the Included Articles

Author (Year)	Domain 1: Patient Selection (Risk of Bias/ Applicability Concern)	Domain 2: Index Test (Risk of Bias/ Applicability Concern)	Domain 3: Reference Standard (Risk of Bias/ Applicability Concern)	Domain 4: Flow and Timing (Risk of Bias)
Wang Q (2012)	Low/Low	Unclear/Low	Low/Low	Low
Liu GH (2013)	Low/Low	Low/Low	Low/Low	Low
Luo X (2013)	Low/Low	Unclear/Low	Low/Low	Unclear
Wang J (2014)	Low/Low	Low/Low	Low/Low	Low
Zheng G (2014)	Low/Low	Unclear/Low	Low/Low	Low
Chang PY (2016)	Low/Low	Low/Low	Low/Low	Low
Liu HN (2018)	Unclear/Low	Unclear/Low	Low/Low	Low
Fu F (2018)	Low/Low	Low/Low	Low/Low	Low
Fathi S (2025)	Low/Low	Unclear/Low	Low/Low	Unclear
Shi Y (2020)	Low/Low	Low/Low	Low/Low	Low
Hassan E (2020)	Low/Low	Unclear/Low	Low/Low	Low
Said E (2017)	Low/Low	Low/Low	Low/Low	Unclear
Zaki A (2022)	Low/Low	Low/Low	Low/Low	Low
Elshafei A (2017)	Low/Low	Unclear/Low	Low/Low	Unclear
Fellizar A (2023)	Low/Low	Low/Low	Low/Low	Low
Elaguizy M (2020)	Low/Low	Low/Low	Low/Low	Low

Lastly, a comparison between single miRNA-92a and miRNA-92a-related circulating panels (multiple) revealed negligible differences. Both subgroups achieved similar pooled AUC values (0.87), and sensitivity and specificity were broadly comparable. Nevertheless, despite this apparent consistency, significant heterogeneity also persisted in the AUC, PLR, and logDOR parameters.

Applicability of miRNAs in Clinical Use

Using Fagan's nomogram analysis, the diagnostic utility of miR-92a for CRC was assessed. A positive test result ($LR^+ = 9$) raised the post-test probability to 75% at a pre-test probability of 25%, whereas a negative test result ($LR^- = 0.15$) decreased the post-test probability to 5%. The post-test probability rose to 90% for a positive result and dropped to 13% for a negative result when the pre-test probability was set at 50%. The equivalent post-test probabilities were 31% for a negative result and 96% for a positive result with a higher pre-test probability of 75%. As shown by Fagan's nomogram

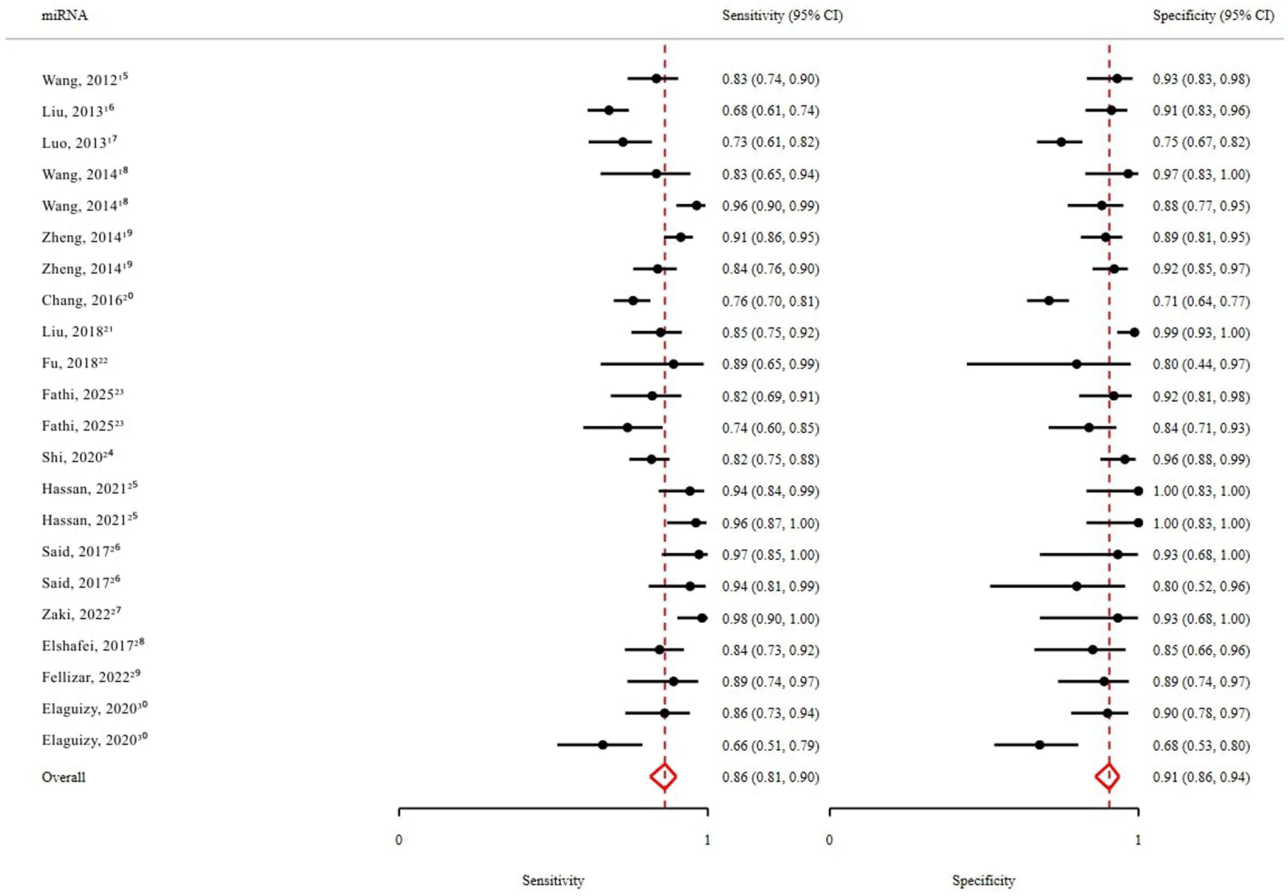

Figure 2 Forest plot of pooled sensitivity and specificity.

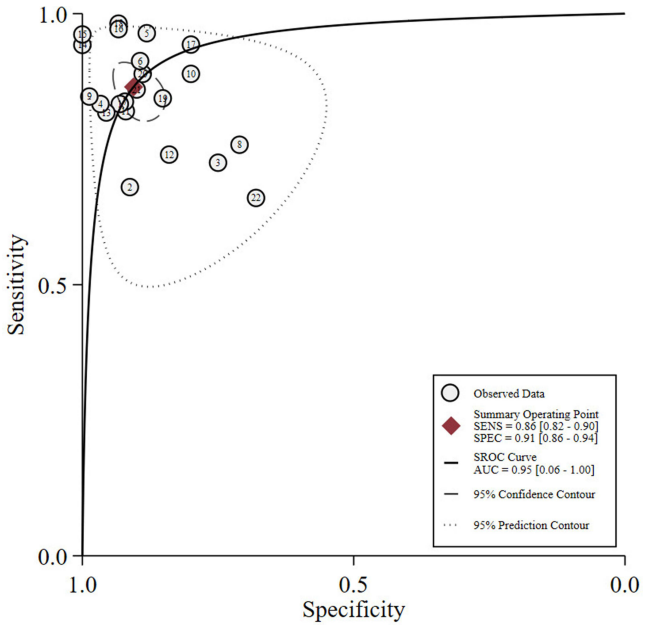

Figure 3 Summary ROC (SROC) curve of miRNA-92a biomarkers.
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve.

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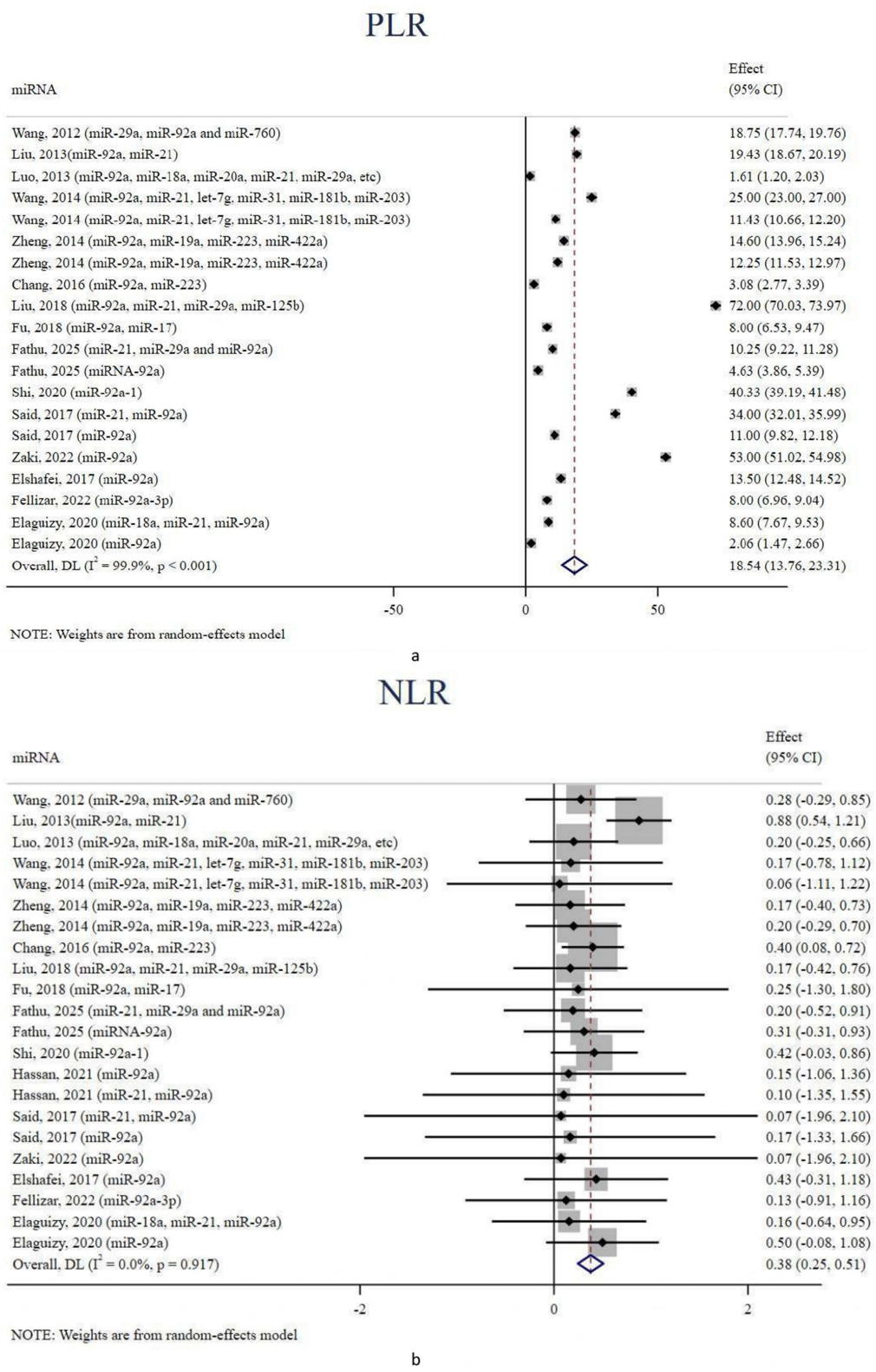

Figure 4 Diagnostic performance estimates of circulating miRNA-92a and related panels: (**a**) negative likelihood ratio (NLR), (**b**) positive likelihood ratio (PLR).

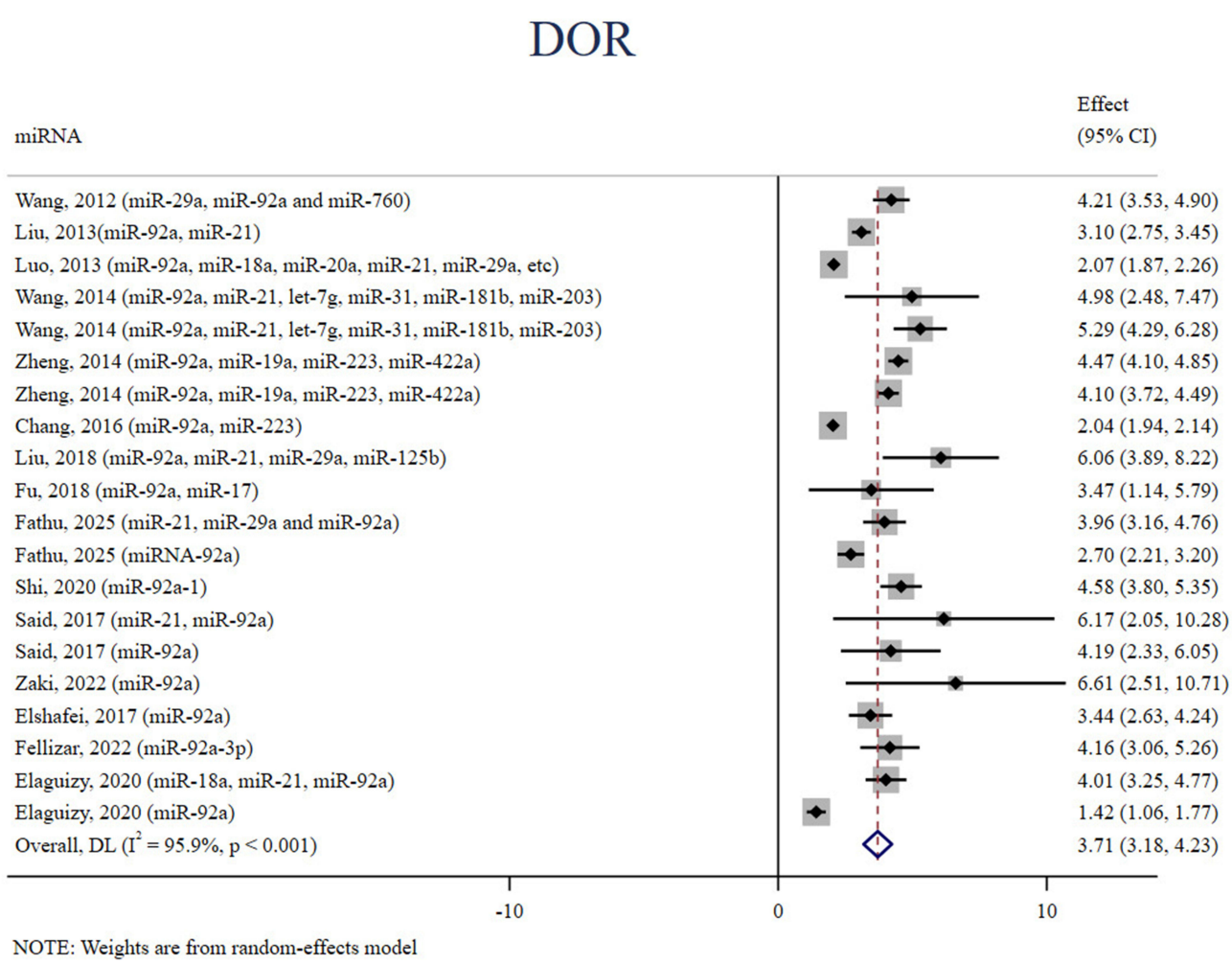

Figure 5 Forest plot of pooled log-transformed diagnostic odds ratio (logDOR).

(Figure 6), these findings suggest that miR-92a significantly affects changing post-test probabilities over a range of baseline risks.

Publication Bias

The Deek's funnel plot asymmetry test was used to determine whether publication bias was present in studies evaluating the diagnostic accuracy of miRNA-92a for colorectal cancer. A p-value of 0.06 was found in the results (*p-value*>0.05), indicating that the included studies do not appear to have any substantial indication of publication bias (Figure 7). Although the p-value is relatively close to the threshold, it remains above the conventional cutoff, supporting the overall reliability of the pooled diagnostic estimates presented in this meta-analysis.

Discussion

This diagnostic meta-analysis highlights the promising potential of miRNA-92a as a diagnostic biomarker of CRC. miRNA-92a showed superior diagnostic performance in 22 studies with more than 3300 participants, with a pooled sensitivity of 86% and specificity of 91%. Its clinical significance is further supported by an AUC value of 0.87, indicating that miRNA-92a and miRNA-92a-related circulating panels are useful for differentiating between CRC patients and healthy individuals.

The high PLR value (18.54) of miRNA-92a, which shows that CRC patients have a nearly 19-fold higher chance of testing positive than healthy controls, further supports the diagnostic power of this biomarkers. On the other hand, when

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Table 4 Subgroup Analyses of Studies Evaluating Circulating miRNA-92a and miRNA-92a-Related Circulating Panels for the Diagnosis of Colorectal Cancer

Subgroup	Number of Studies	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PLR (95% CI)	NLR (95% CI)	logDOR (95% CI)
Country							
China	10	83% (0.770.88)	91% (0.850.95)	0.87* (0.830.91)	22.46* (14.3730.55)	0.41 (0.230.59)	4.13* (3.195.07)
Egypt	8	92% (0.840.96)	92% (0.820.96)	0.90* (0.850.95)	20.33* (9.4931.16)	0.33 (0.020.67)	3.74* (2.225.25)
Sample type							
Plasma	4	80% (0.730.85)	83% (0.700.91)	0.81* (0.720.89)	7.84* (2.7812.89)	0.32 (0.080.55)	2.85* (2.273.43)
Serum	18	89% (0.830.93)	92% (0.880.95)	0.89* (0.860.93)	23.20* (16.2830.12)	0.43 (0.260.60)	4.11* (3.324.89)
Sample size							
≥100	13	81% (0.760.86)	89% (0.820.93)	0.84* (0.800.88)	16.81* (11.1522.47)	0.40 (0.260.54)	3.55* (2.954.14)
<100	9	93% (0.880.95)	92% (0.860.96)	0.93* (0.900.96)	21.76* (11.8031.73)	0.23 (0.170.63)	3.89* (3.324.46)
miRNA number							
Single	8	8 87% (0.780.93)	90% (0.810.95)	0.87* (0.810.93)	18.91* (7.9529.87)	0.37 (0.110.63)	3.51* (2.394.63)
Multiple	14	14 86% (0.800.90)	91% (0.850.96)	0.87* (0.830.91)	18.34* (12.8623.81)	0.38 (0.230.53)	3.86* (3.204.52)

Notes: * Significant heterogeneity: $I^2 > 55\%$ and $p < 0.05$.

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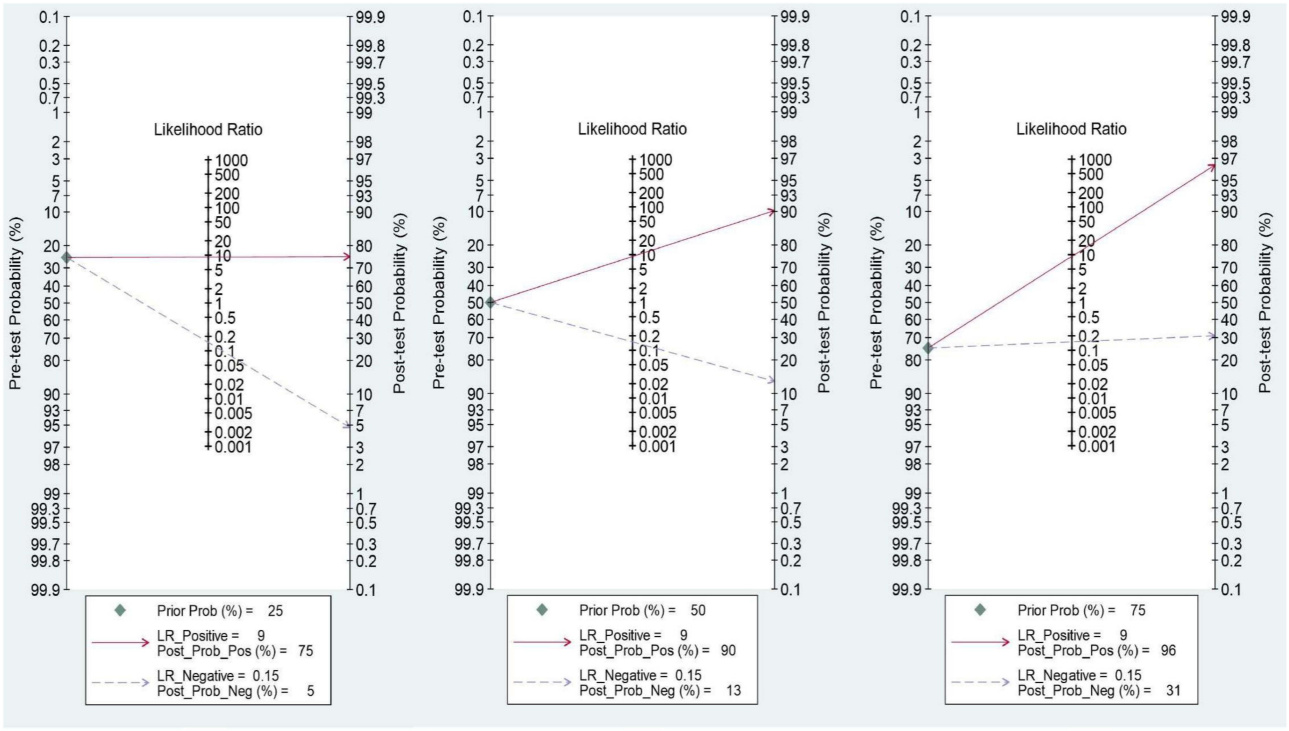

a b c

Figure 6 Fagan's nomogram showing post-test probabilities: (**a**) 25% (**b**) 50% (**c**) 75%.

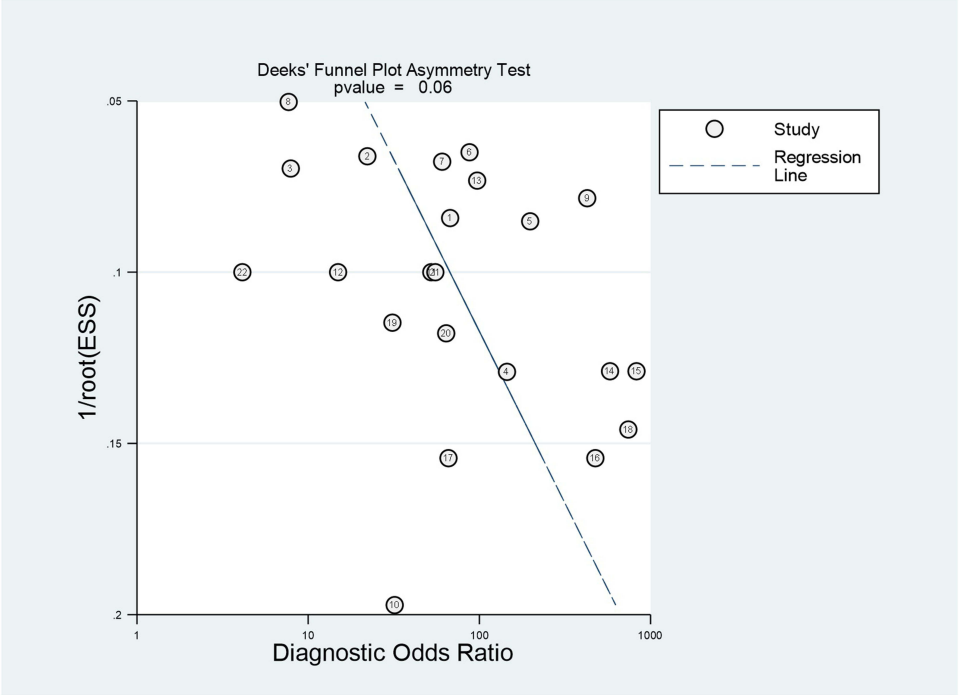

Figure 7 Deek's funnel plot asymmetry test for publication bias.

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the test result is negative, the NLR value (0.38) indicates a moderate capacity to rule out the disease. These results are consistent with earlier research showing that miRNAs have significance for detecting CRC because they identify early molecular changes linked to the initiation and spread of tumors.[15,31]

Subgroup analyses further illuminate factors contributing to heterogeneity across studies. Notably, serum-based miRNA-92a consistently outperformed plasma-based testing in both sensitivity and specificity, possibly due to differences in sample stability or miRNA abundance across biological matrices. Additionally, geographic variability was observed, with studies from Egypt showing slightly better diagnostic outcomes than those from China, although both regions reported high diagnostic accuracy. This discrepancy could reflect variations in study design, patient selection, or miRNA expression influenced by genetic or environmental factors.[32,33]

Importantly, further stratification based on biomarker type revealed that both single miRNA-92a and miRNA-92a-related circulating panels (multiple) demonstrated nearly identical diagnostic performance, each achieving an AUC of 0.87. Although multiple-marker panels showed a slightly higher specificity (91% vs 90%) and marginally lower NLR (0.38 vs 0.37), these differences were not clinically significant. Moreover, the diagnostic odds ratios were highly comparable (3.51 for single miRNA vs 3.86 for multiple), as were the positive likelihood ratios (18.91 vs 18.34), underscoring the robust diagnostic capacity of miR-92a alone. These findings suggest that miRNA-92a, even without additional markers, is sufficiently accurate as a standalone biomarker for CRC diagnosis. Given its simplicity, lower cost, and minimal assay complexity compared to combination panels, the use of miRNA-92a alone may offer practical advantages for implementation in routine clinical settings, particularly in resource-limited environments.

Interestingly, smaller studies tended to report more favorable diagnostic performance, a trend frequently observed in meta-analyses and potentially indicative of small-study effects or selective reporting.[34] Despite this, our analysis did not find statistically significant publication bias ($p = 0.06$), suggesting a reasonably balanced representation of available data. However, substantial heterogeneity remained in several key parameters, including PLR, logDOR, and AUC, highlighting the importance of cautious interpretation and the need for further standardization in future research.

In clinical terms, the Fagan nomogram analysis demonstrates that miRNA-92a testing can significantly alter post-test probabilities in various clinical scenarios. For instance, at a pre-test probability of 25%, a positive test raises the likelihood of CRC to 75%, while a negative result decreases it to just 5%. This suggests that miRNA-92a could serve as a valuable triage tool, by supporting clinical decision-making on whether further invasive diagnostic procedures, such as colonoscopy.

Overall, this meta-analysis supports the diagnostic relevance of miRNA-92a for CRC and encourages further large-scale, multicenter trials to validate its performance in routine clinical practice. Moreover, future studies should aim to clarify the influence of confounding variables, such as age, comorbidities, and tumor stage, on miRNA-92a expression to optimize its clinical applicability.

Limitations

Despite the promising results, several limitations should be acknowledged. First, a substantial proportion of the included studies employed non-blinded, case–control designs and used healthy individuals as controls, which introduces spectrum bias and may overestimate diagnostic performance compared with real-world clinical cohorts where symptomatic or high-risk patients are typically evaluated. Second, heterogeneity in sample types, detection platforms, and normalization strategies across studies could influence pooled estimates and reduce the generalizability of the findings.

An additional methodological consideration is the potential overlap with a previous meta-analysis published in 2019, as many of the articles included in our review were published before that year. Although our analysis incorporates updated studies, the overlap may affect comparative interpretation and should be considered when evaluating the incremental contribution of the present review.

Furthermore, although subgroup analyses were conducted, certain populations, such as those with comorbidities, early-stage disease, or specific ethnic backgrounds, were underrepresented, thereby limiting applicability in diverse clinical settings. Geographic imbalance, particularly the predominance of studies from Asia and Africa, may also introduce population-specific biases. Finally, although combination biomarkers demonstrated slight improvements over

single markers, consensus is lacking regarding the optimal miRNA partners to pair with miR-92a, highlighting the need for further standardization and validation through prospective, multicenter trials.

Conclusion

This meta-analysis confirms the superior diagnostic potential of circulating miRNA-92a for colorectal cancer, demonstrating high sensitivity (86%), specificity (91%), and an AUC of 0.87. Its performance as a standalone biomarker was comparable to multi-marker panels, indicating that miRNA-92a alone may be adequate for clinical screening, particularly in resource-limited settings. Overall, the findings support its value as a practical and costeffective candidate for integration into future CRC diagnostic strategies.

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References

1. GLOBOCAN. Global Cancer Observatory. Available from: https://gco.iarc.fr/today/online-analysis-multi-bars. Accessed December 12, 2025.
2. Jafari A, Hosseini FA, Jalali FS. A systematic review of the economic burden of colorectal cancer. *Health Sci Rep*. 2024;7(8):e70002. doi:10.1002/hsr2.70002
3. Tao XY, Li QQ, Zeng Y. Clinical application of liquid biopsy in colorectal cancer: detection, prediction, and treatment monitoring. *Mol Cancer*. 2024;23(1):145. doi:10.1186/s12943-024-02063-2
4. Kildusiene I, Dulskas A, Smailyte G. Value of combined serum CEA, CA72-4, and CA19-9 marker detection in diagnosis of colorectal cancer. *Tech Coloproctol*. 2024;28(1):33. doi:10.1007/s10151-023-02873-4.
5. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut*. 2015;64:1637–1649. doi:10.1136/gutjnl-2014-309086
6. Zhang C, Sun C, Zhao Y, et al. Overview of MicroRNAs as diagnostic and prognostic biomarkers for high-incidence cancers in 2021. *Int J Mol Sci*. 2022;23(19):11389. doi:10.3390/ijms231911389
7. Chen X, Ba Y, Ma L, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res*. 2008;18:997–1006. doi:10.1038/cr.2008.282
8. Bartoszewska E, Misiąg P, Czapla M, et al. The role of omicroRNAs in lung cancer: mechanisms, diagnostics and therapeutic potential. *Int J Mol Sci*. 2025;26(8):3736. doi:10.3390/ijms26083736
9. Li M, Guan X, Sun Y, et al. miR-92a family and their target genes in tumorigenesis and metastasis. *Exp Cell Res*. 2014;323(1):1–6. doi:10.1016/j.yexcr.2013.12.025
10. Yang X, Zeng Z, Hou Y, et al. MicroRNA-92a as a potential biomarker in diagnosis of colorectal cancer: a systematic review and meta-analysis. *PLoS One*. 2014;9(2):e88745. doi:10.1371/journal.pone.0088745
11. Peng Q, Shen Y, Lin K, Zou L, Shen Y, Zhu Y. Identification of microRNA-92a and the related combination biomarkers as promising substrates in predicting risk, recurrence and poor survival of colorectal cancer. *J Cancer*. 2019;10(14):3154–3171. doi:10.7150/jca.30306
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
13. Hasani F, Masrour M, Jazi K, et al. MicroRNA as a potential diagnostic and prognostic biomarker in brain gliomas: a systematic review and meta-analysis. *Front Neurol*. 2024;15:1357321. doi:10.3389/fneur.2024.1357321
14. Birru ABA, Cuandra KN. Comprehensive analysis of the potential of microRNAs as novel diagnostic biomarkers of placenta accreta spectrum: a systematic review and meta-analysis. *J Pharm Pharmacogn Res*. 2025;13(4):1265–1274. doi:10.56499/jppres24.2244_13.4.1265
15. Wang Q, Huang Z, Ni S, et al. Plasma miR-601 and miR-760 are novel biomarkers for the early detection of colorectal cancer. *PLoS One*. 2012;7:e44398. doi:10.1371/journal.pone.0044398
16. Liu GH, Zhou ZG, Chen R, et al. Serum miR-21 and miR-92a as biomarkers in the diagnosis and prognosis of colorectal cancer. *Tumour Biol*. 2013;34:2175–2181. doi:10.1007/s13277-013-0753-8
17. Luo X, Stock C, Burwinkel B, Brenner H. Identification and evaluation of plasma microRNAs for early detection of colorectal cancer. *PLoS One*. 2013;8:e62880. doi:10.1371/journal.pone.0062880
18. Wang J, Huang SK, Zhao M, et al. Identification of a circulating microRNA signature for colorectal cancer detection. *PLoS One*. 2014;9:e87451. doi:10.1371/journal.pone.0087451
19. Zheng G, Du L, Yang X, et al. Serum microRNA panel as biomarkers for early diagnosis of colorectal adenocarcinoma. *Br J Cancer*. 2014;111:1985–1992. doi:10.1038/bjc.2014.489
20. Chang PY, Chen CC, Chang YS, et al. MicroRNA-223 and microRNA-92a in stool and plasma samples act as complementary biomarkers to increase colorectal cancer detection. *Oncotarget*. 2016;7:10663–10675. doi:10.18632/oncotarget.7119
21. Liu HN, Liu TT, Wu H, et al. Serum microRNA signatures and metabolomics have high diagnostic value in colorectal cancer using two novel methods. *Cancer Sci*. 2018;109:1185–1194. doi:10.1111/cas.13514

22. Fu F, Jiang W, Zhou L, Chen Z. Circulating exosomal miR-17-5p and miR-92a-3p predict pathologic stage and grade of colorectal cancer. *Transl Oncol*. 2018;11(2):221–232. doi:10.1016/j.tranon.2017.12.012
23. Fathi S, Aazzane O, Guendaoui S, et al. A miRNA signature for non-invasive colorectal cancer diagnosis in Morocco: miR-21, miR-29a and miR-92a. *Non-Cod RNA*. 2025;11(2):26. doi:10.3390/ncrna11020026
24. Shi Y, Liu Z. Serum miR-92a-1 is a novel diagnostic biomarker for colorectal cancer. *J Cell Mol Med*. 2020;24(15):8363–8367. doi:10.1111/jcmm.15282
25. Ahmed Hassan E, As E-DAE-R, Mohammed Kholef EF, W A-EE. Potential role of plasma miR-21 and miR-92a in distinguishing between irritable bowel syndrome, ulcerative colitis, and colorectal cancer. *Gastroenterol Hepatol Bed Bench*. 2020;13(2):147–154.
26. Said E, Zidan A, Nawar A, et al. Circulating Micro RNA-21 and −92a as biomarkers of colorectal cancer. *Afro-Egypt J Infect Endem Dis*. 2017;7(4):247–257. doi:10.21608/aeji.2017.17839
27. Zaki A, Fawzy A, Akel SY, Gamal H, Elshimy RAA. Evaluation of microRNA 92a expression and its target protein bim in colorectal cancer. *Asian Pac J Cancer Prev*. 2022;23(2):723–730. doi:10.31557/APJCP.2022.23.2.723
28. Elshafei A, Shaker O, Abd El-motaal O, Salman T. The expression profiling of serum miR-92a, miR-375, and miR-760 in colorectal cancer: an Egyptian study. *Tumor Biol*. 2017;39(6). doi:10.1177/1010428317705765
29. Fellizar A, Refuerzo V, Ramos JD, Albano PM. Expression of specific microRNAs in tissue and plasma in colorectal cancer. *J Pathol Transl Med*. 2023;57(3):147–157. doi:10.4132/jptm.2022.02.19
30. Elaguizy M, Sheta M, Ibrahim N, Eltaweel A, Mostafa A. Serum microRNA-18a, MicroRNA-21 and microRNA-92a as diagnostic markers in colorectal cancer patients. *J BUON*. 2020;25(3):1443–1448.
31. Huang Z, Huang D, Ni S, Peng Z, Sheng W, Du X. Plasma microRNAs are promising novel biomarkers for early detection of colorectal cancer. *Int J Cancer*. 2010;127(1):118–126. doi:10.1002/ijc.25007
32. Zaher DM, Mahmoud NM, Farag MM, El-Hefnawy SH, El-Mezayen HA. Circulating miRNA-92a and miRNA-21 as potential noninvasive biomarkers for colorectal cancer. *Mol Diagn Ther*. 2020;24(4):409–420.
33. Ma Y, Zhang P, Wang F, et al. Elevated oncofetal miR-92a expression regulates cell proliferation and apoptosis in colorectal cancer by targeting BCL2L11. *Mol Cancer*. 2013;12(1):1–12. doi:10.1186/1476-4598-12-1
34. Wu CW, Ng SS, Dong YJ, et al. Detection of miR-92a and miR-21 in stool samples as non-invasive biomarkers for colorectal cancer. *Clin Cancer Res*. 2012;18(18):4801–4810.