REVIEW

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# Diagnostic and Prognostic Value of *miR-451* Expression in Colorectal Cancer: A Meta-Analysis

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## Abstract

**Background:** The *miR-451* has been reported to play an important role in colorectal cancer (CRC) pathogenesis and can be a pivotal diagnosis biomarker of CRC. Given the contradictions in the diagnosis value of the *miR-451* in patients with CRC, deciphering the diagnostic/prognostic role of this miRNA in CRC will support the identification of a novel therapeutic target for CRC. Therefore, in the present meta-analysis, we evaluated the diagnostic value of *miR-451* in CRC patients. **Materials and methods:** The electronic databases of Embase, PubMed, ISI Web of Science, and Scopus systematically searched for relevant studies. The odds ratio (OR) with a 95% confidence interval (CI) was calculated to evaluate the association between *miR-451* family expression and diagnosis of colorectal cancer. The parameters including sensitivity, specificity, and area under the curve (AUC) were obtained. The quality of evidence was evaluated using the Newcastle-Ottava Scale (NOS). **Results:** This study involved 510 patients (45% female and 55% male) with CRC. The pooled analysis of the studies showed a significant association between low expression levels of *miR-451* in patients with CRC (OR = 7.59; 95% CI 2.39 – 24.07; p = 0.001). The overall sensitivity and specificity were 0.95 (0.61 – 1) and 0.83 (0.43 – 0.99), respectively. The pooled AUC was 0.97 (0.88 – 1; p < 0.006). Results showed if the pre-test probability is 50% for a patient, the post-test probability will be 85%. The indices demonstrated the high potency of *miR-451* as a diagnostic biomarker in patients with CRC. No publication bias was observed using the Begg's (p=0.85) and Egger's tests (p=0.45). **Conclusion:** A strong relationship between the low expression levels of *miR-451* and CRC progression was observed. This finding suggests the *miR-451* family may be helpful as a potential biomarker for the earlier diagnosis of colorectal cancer.

**Keywords:** Colorectal Cancer- *miR-451*- Meta-analysis- Diagnostic Biomarker- prognosis

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## Introduction

Cancer is one of the leading causes of mortality worldwide. Colorectal cancer (CRC) is considered the third most common cancer around the world and is estimated to cause more than 1.1 million deaths by 2030 [1]. On the other hand, colon cancer is one of the most common gastrointestinal malignancies [2]. Although the diagnosis and treatment of CRC have greatly improved, global evidence shows that its high mortality rate is not satisfactory for patients with CRC due to cancer recurrence, metastasis, and resistance to radiation and chemotherapy [1]. Therefore, more studies are required to decipher the underlying molecular mechanisms and new biomarkers involved in the initiation and progression of CRC. Recent investigations have reported the regulatory role of miRNAs in the pathogenesis of CRC [3].

MicroRNAs (miRNAs) are a class of endogenous non-coding RNAs consisting of 20-25 nucleotides, which play a key role in various types of disease development [4]. After the discovery of miRNA function, the role of miRNAs in different diseases, especially cancer has been widely investigated in recent decades [5, 4]. A large body of findings indicates that miRNAs are key players in most types of human cancers [6]. Recent cancer-related research focusing on miRNAs has characterized a large number of miRNAs that are frequently dysregulated in cancer. For instance, a number of miRNAs have been evaluated in preclinical studies and clinical trials [7]. This evidence showed the potential of miRNAs as

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diagnostic and prognostic biomarkers for cancer. In this regard, dysregulation and the roles of miRNAs in several biological processes have been found to be related to CRC [8, 9]. In addition, there is a vast number of findings supporting the main role of miRNAs in metastasis, cell proliferation, and apoptosis, which are considered hallmarks of CRC development [10]. In the previous decade, it has been investigated the differential expression profile of miRNAs in CRC. For example, a study reported that upregulation of miR-21 increased cell proliferation and suppressed apoptosis against the treatment of the chemotherapeutic agent Fluorouracil (5-FU) in an HT29 CRC cell [11, 12]. In addition, *miR-451* has been recently introduced as a novel biomarker and potential therapeutic target for cancer [13]. For example, PHUA et al. reported the utility of a global miRNA (including fecal miR-223 and *miR-451*) screening approach in elucidating diagnostic markers of CRC [14]. In another study, Wu et al., 2021, found that *miR-451* suppresses the malignant characteristics of CRC by targeting SAMD4B in vivo and in vitro. Therefore, *miR 451*/SAMD4B axis might serve as a new therapeutic target in patients with CRC. In this regard, Mamoori et al. have shown that the *miR-451* has tumor suppressor effects in-vitro, which can inhibit the cancer-related signaling pathways in colon cancer [15]. However, miRNA profiling might be a novel approach for the diagnosis of most types of tumors, including CRC.

Accumulating data have revealed the important role of *miR-451* in CRC pathogenesis. Given the many contradictions in the diagnosis value of the *miR-451* in CRC patients, clarifying the biomarker role of this miRNA in CRC will support the discovery of a novel and potential therapeutic target for CRC. Therefore, in the present meta-analysis, the data collected from studies and analyzed.

## Materials and Methods

*Search Strategy and Eligibility Criteria*

Following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we did a systematic search directed by searching the PubMed, Embase, ISI Web of Science, and Scopus databases to identify relevant studies published before December 2023 that reported the prognostic value of *miR-451* expression in the tissue/serum/plasma of patients with CRC. The following Mesh terms were used: ("Colon cancer" AND "microRNA-451") OR ("Colorectal cancer" AND "microRNA-451) OR ("Rectal cancer" AND "*miR-451*). Additionally, all references of retrieved publications were searched to select relevant articles. Duplicate papers were removed, and articles were reviewed by two independent reviewers (N.AD and M.K).

We selected only papers that reported hazard ratios (HR), odds ratios (OR), and confidence intervals (CI) for the detailed investigation. We excluded publications that met any of the following criteria: i) conference abstracts; ii) not published in English; iii) full text not available; iv) review articles, letters, and meta-analysis; v) the expression of miR-21 was assessed in non-human samples; vi) studies that lacked sufficient, valuable and quality data.

*Data Extraction*

The information extracted from the chosen articles was organized in an Excel worksheet that included data about the first author's name, publication year, country, study design, clinical stage of cancer, sample type and count, mean age of participants, clinicopathological characteristics, *miR-451* family, number of patients with CRC, *miR-451* family cutoff, method for evaluating *miR-451* family, follow-up time, outcome of prognosis, HR, 95% confidence interval, and NOS score of each included study.

*Quality assessment*

The eligibility criteria of included studies were separately employed by two individual reviewers who then proceeded to data collection (N.AD and M.K). The quality assessment was performed based on the Newcastle–Ottawa scale (NOS) (29). A NOS score <4, between 4-to-6, and a NOS score ≥7 were considered a study with low quality, moderate quality, and high-quality study, respectively.

*Statistical analysis*

We used the diagnostic odds ratio (DOR) and 95% CI to quantitatively determine the diagnostic value of the *miR-451* family in colorectal cancer. Heterogeneity among studies was assessed using the Q test and the Higgins I-square (P <0.1, values <25%, 25%-50%, and >50% were set to indicate mild, moderate, and significant heterogeneity, respectively) [16]. If $I^2 > 50\%$, the DerSimonian and Laird random-effect models were used to obtain the ORs. We also applied Begg's rank correlation test and Egger's regression asymmetry test to evaluate the potential publication bias produced by the funnel plot [17]. Sensitivity analysis was also performed to evaluate the impact of removing each study using the "leave-one-out method". We obtained the following parameters including sensitivity, specificity, positive likelihood ratios (PLRs), and negative likelihood ratios (NLRs) in this meta-analysis. In addition, we assessed the area under the receiver operator characteristic curve and Fagan plots to examine the diagnostic power of *miR-451*. The area under the curve (AUC) of 1.0 means perfect diagnostic ability, whereas, an AUC close to 0.5 shows a weak diagnostic ability [18]. All analyses were performed using MedCalc statistical software (version 22.014). A value of <0.05 was considered statistically significant.

## Results

*Search*

A literature search was performed to obtain the eligible studies in this meta-analysis by two investigators separately. In total, 2 studies from Embase, 40 from PubMed, 30 from the Web of Science, and 28 from the Scopus database were extracted. Of these, 45 articles were duplicates, which were removed. The remaining 55 articles were checked by title, abstract, and full- text. Out of the 55 articles screened. 49 articles were excluded

as they did not meet the inclusion criteria as follows: 20 articles were published as reviews, editorials, and letters, 9 articles did not measure the level of *miR-451* as the main primary outcome, 11 articles were performed in animal and in vitro models, 4 articles were not reported as English language, 5 articles were also excluded due to had no sufficient information for data extraction. Thus, based on the predefined inclusion and exclusion criteria, only 6 articles were eligible for the quantitative analysis in this meta-analysis. The pathway of the study selection according to the PRISMA flowchart is shown in Figure 1.

*Characteristics of the eligible studies*

The baseline characteristics of the accessible studies are summarized in Table 1. Six studies were eligible for the meta-analysis. The primary characteristics of selected articles are included as follows: Out of these 6 studies, 3 studies were performed in China, leaving 3 studies were conducted in Egypt, Singapore, and Australia respectively. All of the articles measured the expression *miR-451* compared to control by QRT-PCR. In addition, 3 articles evaluated the expression level of *miR-451* in colorectal cancer tissue samples, 2 articles assessed *miR-451* expression in serum, and one study in feces. 5 studies reported *miR-451* levels in patients with stage II colorectal cancer and one study reported in patients with stage III colorectal cancer. Of 510 patients with colorectal cancer were 45% female and 55% male. The NOS score of all articles was ≥ 7 except for Xu et al., which had an NOS score of 6 (Table 2).

*Quantitative analyses*

*Diagnostic value of miR-451 in CRC*

For 510 participants in 6 studies reporting the diagnostic role of *miR-451* in patients with colorectal cancer, significant heterogeneity was observed ($I^2 = 85\%$,

Table 1. Main Characteristics of Eligible Studies

| Author (year) | Country | sample source | Methods of examination | Sample size (case) | Sample size (control) | M/F | Total | TP | FP | FN | TN |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Salah M et al., (2020) | Egypt | Serum | qRT-PCR | 37 | 30 | 15/22 | 67 | 28 | 1 | 9 | 29 |
| Phua L et al., (2014) | Singapore | Feces | qRT-PCR | 17 | 18 | 13/4 | 45 | 15 | 0 | 2 | 28 |
| Guo D et al., (2022a) | China | Serum | qRT-PCR | 159 | 94 | 91/68 | 159 | 28 | 49 | 37 | 45 |
| Guo D et al., (2022b) | China | Tissue | qRT-PCR | 159 | 92 | 89/70 | 159 | 28 | 48 | 39 | 44 |
| Xu K et al.,(2017) | China | Tissue | qRT-PCR | 68 | 24 | 38/30 | 68 | 36 | 8 | 3 | 8 |
| Mamoori et al.,(2016) | Australia | Tissue | qRT-PCR | 70 | 41 | 35/35 | 70 | 25 | 4 | 39 | 2 |

qRT-PCR, Quantitative real-time PCR; M/F, Male/female; TP, True positive; FP, False positive; FN, False negative; TN, True negative.

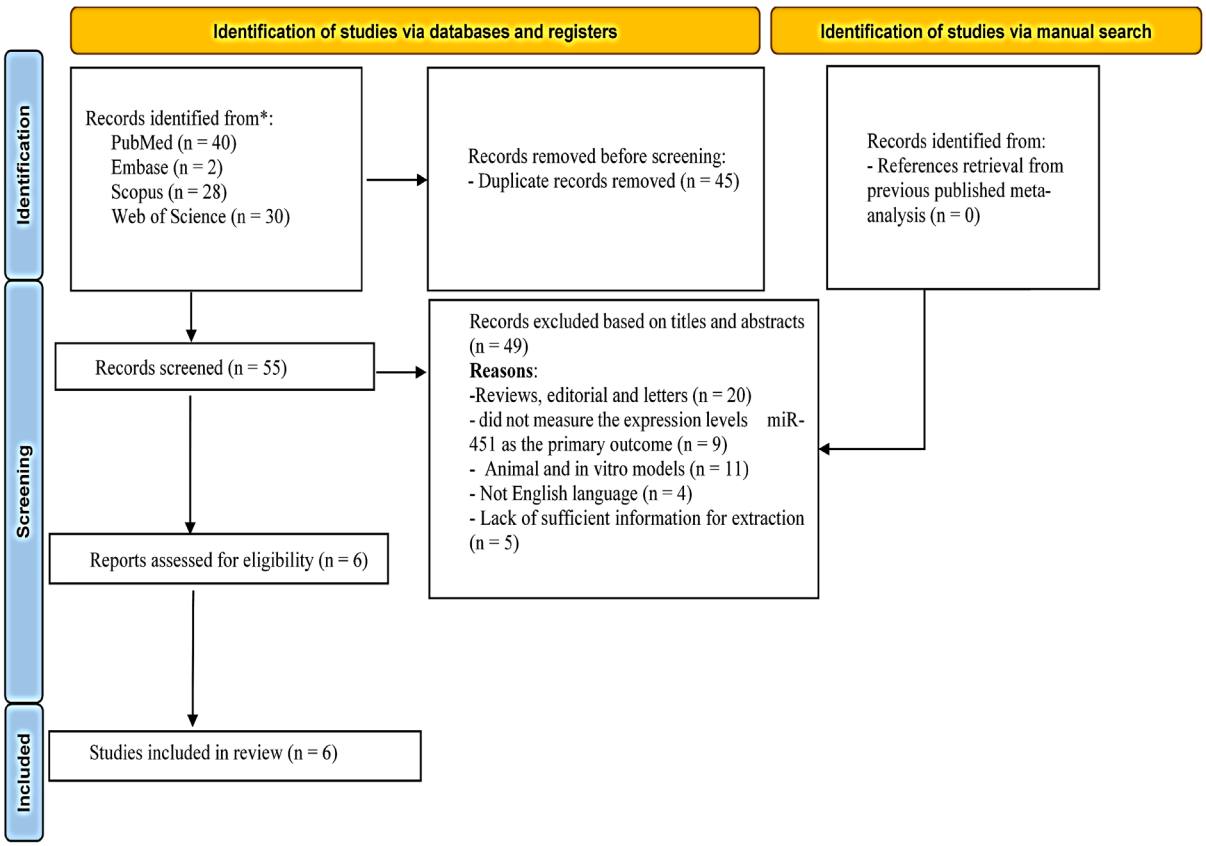


Figure 1. Flow Diagram of Studies Selection

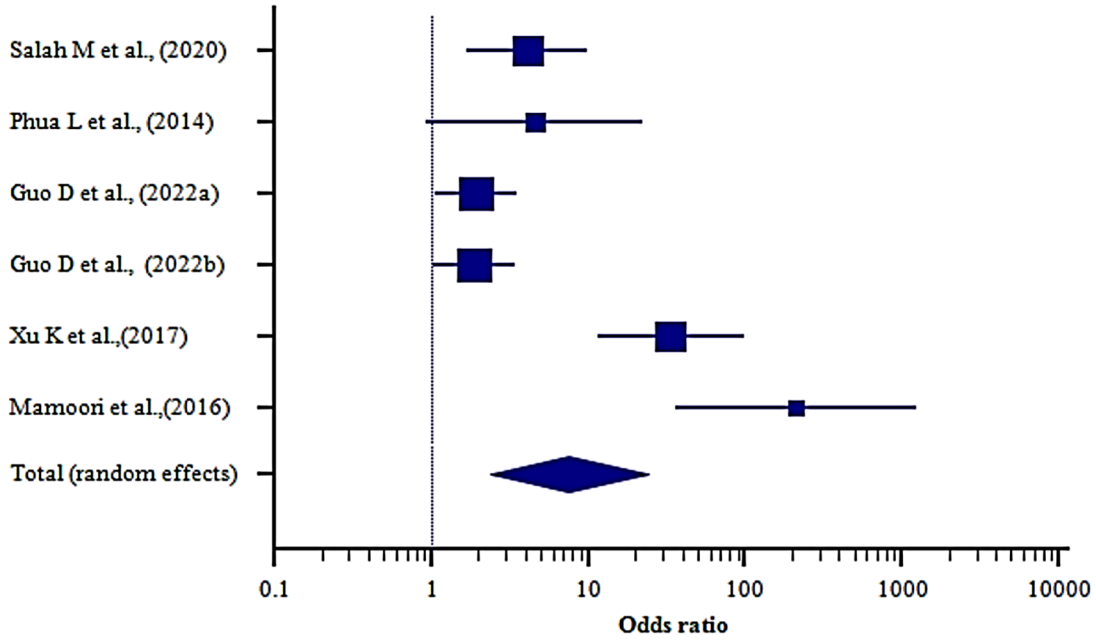


Figure 2. Forest Plot of Overall Diagnostic Odds Ratio of *miRNA-451* for Colorectal Cancer

$p < 0.001$). So, the random effect model was used to calculate all analyses in this meta-analysis. The summary diagnostic odds ratio indicated a strong association between the low expression levels of *miR-451* and CRC progression (OR = 7.59; 95% CI 2.39 – 24.07; p = 0.001) (Figure 2). The overall sensitivity and specificity were 0.95 (0.61 – 1) and 0.83 (0.43 – 0.99) respectively. The pooled area under the curve was 0.97 (0.88 – 1; $p < 0.006$). This index shows the diagnostic power of *miR-451* was high (Figure 3). In addition, we performed an estimation of the results of how much a diagnostic test alters the probability that a patient has a disease using Fagan's nomogram. Our findings showed that if the pre-test probability is 50% for a patient, the post-test probability will be 85% with a PLR of 6 and 15% with an NLR of 0.19 (Figure 4). All our findings demonstrated that *miR-451* had a high diagnostic power in detecting CRC.

*Sensitivity analysis*

Sensitivity analysis was conducted using the "leave-one-out" method. In this method, to examine the influence of each study on the pooled effect size, each study was removed in turn. Removing each study did not affect the pooled results. Thus, we had a robust conclusion that it's reliable to interpret.

*Publication bias*

We used the funnel plot, Begg's rank correlation, and Egger's linear regression tests to evaluate the publication bias in this meta-analysis. As presented in Figure 5, the funnel plot was symmetric and the results of Begg's

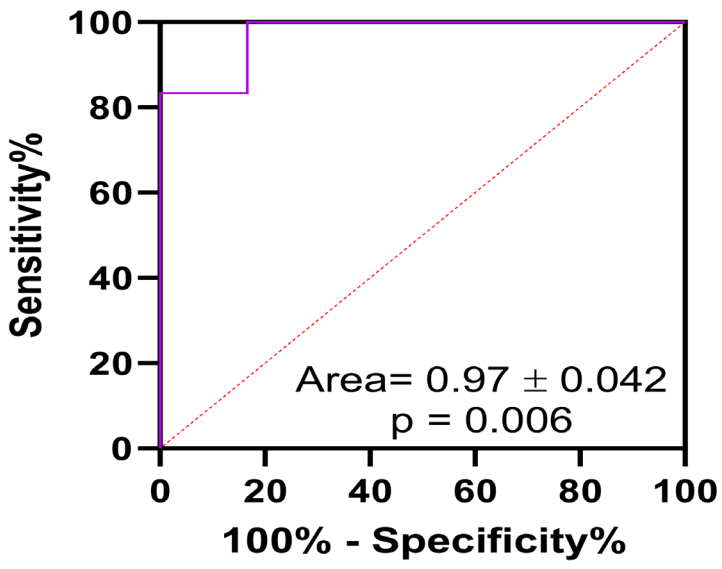


Figure 3. The Receiver Operating Characteristic Curve of *miRNA-451* for Colorectal Cancer

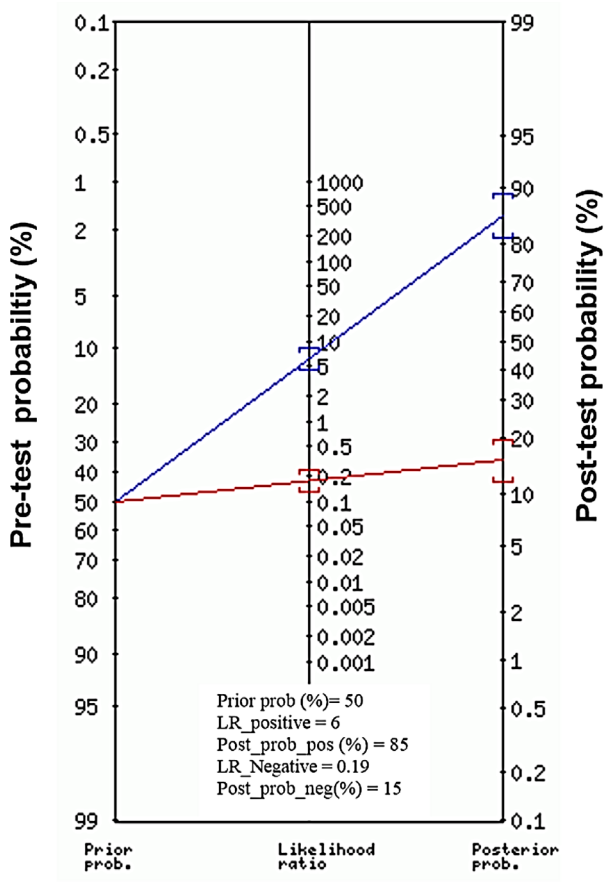


Figure 4. Fagan Diagram Evaluating the Pooled Diagnostic Value of *miRNA-451* for Colorectal Cancer (If the pre-test probability is 50% for a patient, the post-test probability will be 85% with a PLR of 6 and 15% with an NLR of 0.19)

(p = 0.85) and Egger's (p = 0.45) were not significant. Thus, no significant publication bias was observed for the present meta-analysis.

## Discussion

MicroRNAs (miRNAs) are a family of endogenous small non-proteins encoding RNA molecules that exert their repressive functions by binding directly to the 3'-untranslated regions (3'-UTR) of the target gene [19]. MiRNAs are involved in several biological processes, such as cell development, differentiation, and apoptosis [20, 21]. On the other hand, due to the central role of miRs in the regulation of tumorigenesis, they have attracted wide attention as potential therapeutic targets or disease diagnostic and prognostic biomarkers in cancer [22, 23]. Dysregulation of miRNA expression in human cancers is reported in several investigations and usually is associated with metastasis and elevated malignancy of tumor cells. Some miRNAs are extremely expressed in CRC cells and have an important role in creating a microenvironment that allows the cancer cells to progress. These miRs are known as oncogenic miRs [24]. Recent investigations have found several miRs as diagnostic, prognostic biomarkers in CRC tissues, stool, and serum/plasma [25-27]. On the other hand, drug resistance is also a main barrier to achieving effective cancer therapy. It has been shown that miRs have the ability to predict therapeutic responses, as some miRs

Table 2. Methodological Quality of Identified Studies According to Newcastle-Ottawa Scale (NOS) Checklist.

| Eligible studies | Salah M et al. | Phua L et al. | Guo D et al. | Guo D et al. | Xu K et al. | Mamoori et al. |
|---|---|---|---|---|---|---|
| Is the definition adequate? | ++ | ++ | ++ | ++ | ++ | ++ |
| Representativeness of the cases | + | + | + | + | + | + |
| Selection of controls | + | + | + | + | + | + |
| Definition of controls | + | + | + | + | + | + |
| Comparability of both groups | + | + | + | + | - | - |
| Ascertainment of diagnosis | + | - | + | + | - | - |
| Same ascertainment method for both groups | + | + | + | + | + | + |
| Non-response rate | + | + | - | - | - | + |
| Total scores | 9 | 8 | 8 | 8 | 6 | 7 |

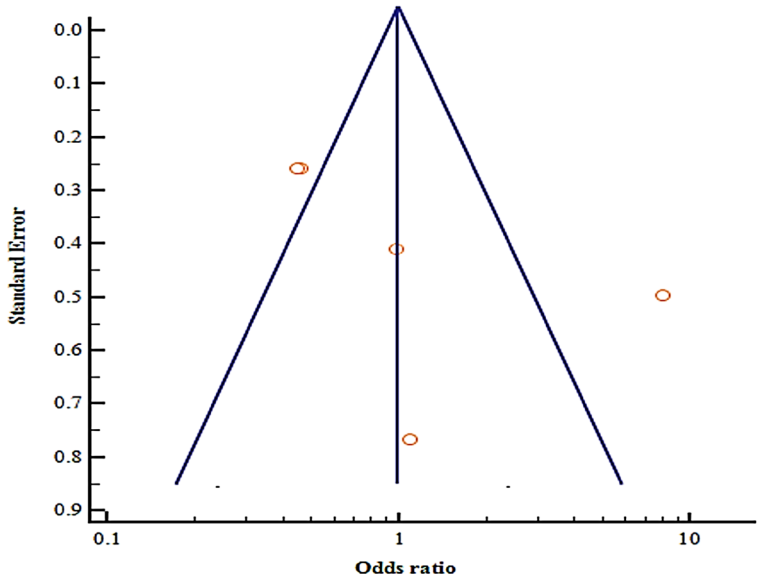


Figure 5. Funnel Plot for Assessing Publication Bias of Included Studies in This Meta-Analysis

have been reported to induce chemoresistance in different malignancies, such as CRC [28-30]. *MiR-451* is a family of microRNAs that are involved in various human cancers. Many previous investigations have shown a clear role of *miR-451* in the proliferation, migration, and invasion of various cancers, including CRC [31, 32]. Apart from that, *miR-451* is involved in the self-renewal, tumorigenicity, and chemoresistance of CRC stem cells [33]. In addition, *miR-451* is related to the inhibition of human CRC Cells via the downregulation of the Pi3k/Akt pathway [34]. Interestingly, it has been found that *miR-451*a affects the radiation sensitivity of colorectal carcinomas [35]. Taken together, these findings indicate that *miR-451* could play a role in the development and progression of CRC, therefore, it could be a novel biomarker associated with CRC. According to this, we performed a meta-analysis to decipher the diagnostic role of *miR-451* associated with CRC.

Given the significant heterogeneity among included studies, the random effect model was performed to calculate all analyses in the current meta-analysis. In the present study current literature, through a meta-analysis demonstrates that *miR-451* levels are significantly lower in patients with colorectal cancer compared to the adjacent normal tissue. As such, the findings from the present study, which confirm that *miR-451* levels are reduced in colorectal cancer patients, correspond with the results from previously published studies, and the results collectively implicate *miR-451* as a diagnostic biomarker in CRC progression. A significant heterogeneity was observed among the included studies. The observed heterogeneity in this meta-analysis might have been due to the decreased number of studies in the analysis.

In addition, to account for the diagnostic value of *miR-451*, we analyzed the sensitivity and specificity of *miR-451* in CRC. these sensitivity and specificity results confirmed the high diagnostic power for *miR-451* in CRC. In addition to the usual analyses, we also performed an estimate of the results of how much a diagnostic test alters a patient's likelihood of disease development by using the Fagan nomogram. The result of this estimation suggested a post-test probability of 85% for a pre-test probability of 50% for a patient according to Figure 4, these findings demonstrated the high potency of *miR-451* as a diagnostic biomarker in patients with CRC.

In the next step, with the sensitivity analysis, we showed that excluding any of the studies did not affect the overall results. Thus, we had a robust conclusion that it's reliable to interpret. In order to explore the publication bias among studies, publication bias was performed by funnel plot as visual and Begg's and Egger's tests as statistical analysis. We found no significant publication bias for the current meta-analysis.

The present meta-analysis has several strengths. This meta-analysis was obtained from the comprehensive data on the diagnostic value of *miR-451* in patients with CRC. The systematic search strategy was very detailed and covered several databases. Statistical analysis indicated no significant publication bias among studies. Evaluation of the methodology quality of the eligible studies using NOS score showed that the most of studies had scores higher than 7. Lastly, our results remained robust in sensitivity analysis. The current meta-analysis has several limitations. The considerable heterogeneity was one of the limitations of the included studies. The relatively small sample size of the primary studies included in the analysis may be another limitation of our study. However, further studies with a larger sample size are needed to confirm these results. This meta-analysis found that low expression of *miR-451* may be a potential biomarker for CRC progression. However, due to the small sample size, the results should be interpreted with caution.

In conclusion, available evidence from included studies in this meta-analysis suggests a potential diagnostic value of *miR-451* in CRC patients. Significant downregulation of *miR-451* in patients with CRC compared with normal

samples supports *miR-451* as an adjunct biomarker to earlier diagnosis of CRC among patients. Further studies are required to validate the diagnostic effect of *miR-451* in the management of the development and progression of CRC.

## Author Contribution Statement

N.AD, and M.K: conceptualization, methodology, investigation, formal analysis, and writing - original draft. H. A, M. RT and N. A: Interpretation, writing - original draft, and writing - review & editing. All the authors have read and approved the final version of the manuscript.

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*Ethical approval*

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1401.010).

*Data availability statement*

The data that support the findings of this study are available in the manuscript and the sources have been cited.

*Conflict of Interest*

The authors declare no conflict of interest.

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