Reproductive Sciences (2020) 27:793–805
https://doi.org/10.1007/s43032-019-00024-5

ORIGINAL ARTICLE

Diagnostic Value of Circulating MicroRNAs for Endometriosis: a Meta-analysis

Ling Zhou[1] · Yan Chen[1] · Jianhua Gao[1] · Sandhya Shankar[2] · Guangmei Zhang[1]

Received: 30 November 2018 / Accepted: 1 April 2019 / Published online: 24 February 2020

Abstract

Endometriosis is a common reproductive system disease worldwide that mainly causes chronic pelvic pain and infertility. Despite its high prevalence, the diagnosis of some patients with endometriosis is delayed for several years, which may be because the gold standard for diagnosis is an expensive and invasive surgical assessment by laparoscopy or laparotomy. Circulating microRNAs (miRNAs) play an important role in a wide range of diseases, including endometriosis, and have been discovered to be potential diagnostic markers. This meta-analysis, which was designed to investigate the diagnostic value of circulating miRNAs for endometriosis, summarizes miRNA articles that met a set of inclusion criteria. Using a bivariate model, we calculated the sensitivities, specificities, and area under the curve (AUC) values of individual miRNAs and miRNA panels. The pooled diagnostic sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the receiver operating characteristic (AUROC) curve were 0.86 (95% CI 0.79–0.90), 0.88 (95% CI 0.80–0.93), 7.05 (95% CI 4.20–11.84), 0.16 (95% CI 11–0.24), and 0.93, respectively. Taken together, these findings indicate that circulating microRNAs may serve as potential noninvasive biomarkers of endometriosis.

Keywords Endometriosis · microRNA · Biomarkers · Meta-analysis

Introduction

When endometrial tissues (glands and stroma) are found outside the uterus, the condition is known as endometriosis. It is one of the most common diseases in women of childbearing age, and the incidence rate has increased significantly in recent years [1–3]. Endometriosis has a variety of clinical manifestations, the most common of which are infertility, pelvic pain, a pelvic mass, and sexual discomfort [4]. Due to the shortage of effective and simplified biomarkers, the fertility of patients with symptoms can be greatly reduced, and they may suffer for many years before their disease is confirmed. A 6–11-year delay often occurs between the onset of the disease and the final diagnosis. The symptoms of endometriosis may show many commonalities with those of a variety of diseases. On average, women consult seven gynecologists before they are diagnosed and before they begin treatment [5]. Histologically, endometriosis is a benign disease, but it is characterized by malignant features, such as hyperplasia, infiltration, metastasis, and a high recurrence rate. This disease is classified as a cancer-like entity by the World Health Organization Histologic Classification of Ovarian Tumors [6–8]. According to Angiolo Gadducci et al., a 2- to 3-fold higher risk of ovarian endometrioid and clear cell carcinoma has been reported in women with endometriosis [9]. If no medical intervention occurs, the condition will continue to progress. The current diagnosis primarily depends on an imaging examination, as serological markers such as CA-125 have poor

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s43032-019-00024-5) contains supplementary material, which is available to authorized users.

✉ Guangmei Zhang
guangmeizhang@126.com

[1] Department of Gynaecology, First Affiliated Hospital, Harbin Medical University, Harbin 150001, Heilongjiang, China

[2] Department of Neurology Biomedical Science, University of Pittsburgh, Pittsburgh, PA 15260, USA

specificity and sensitivity [10, 11]. To date, laparoscopic examination together with biopsy for the histological confirmation of suspicious lesions is the gold standard for diagnosis, but these are invasive and expensive. Therefore, due to the delayed diagnosis, a noninvasive diagnostic approach is urgently needed.

MicroRNAs (miRNAs) are a class of endogenous noncoding RNAs 17-25 nucleotides in length that are capable of participating in a variety of physiological and pathological processes such as cell growth and apoptosis at posttranscriptional levels, and they play an important role in gene regulatory networks [12]. MiRNAs are present extensively in body fluids, and many miRNAs in certain diseases are abnormally expressed and are easy to detect, and thus, they may become novel biomarkers for early noninvasive diagnosis of diseases [13]. Numerous studies have shown that miRNAs regulate various aspects of endometriosis, such as angiogenesis and cell migration [8, 14]. MiRNAs have also been found to be abnormally expressed in endometriotic lesions, tissues, serum, and other body fluids, and their diagnostic value has recently received much attention worldwide [15]. For example, in 2009, RO Burney et al. evaluated the differential expression of miRNAs in the eutopic endometrium of individuals with endometriosis and those without endometriosis. MiR-21-5p was found to be one of the most differentially expressed miRNAs [16]. In addition, Zong wen Liang et al. found that many miRNAs are abnormally expressed in endometriosis, including miR-200c and miR-638 as well as let-7 [17]. The increasing numbers of miRNAs, such as the let-7 family and the miR-200 family, have been identified and reported to show abnormal serological levels in patients with endometriosis, and such miRNAs can be used as novel serological markers [18, 19]. Therefore, we designed a meta-analysis to verify whether circulating miRNAs can serve as potential diagnostic markers for endometriosis.

Results

Search Results and Characteristics of the Eligible Studies

We searched the PubMed, Embase, and Cochrane library databases up to July 30, 2018, to select articles that met the criteria. In all, 111 studies were selected, of which 34 studies were duplicates. Thirty-eight articles remained after removing letters, reviews, editorials, nonclinical studies, and irrelevant articles by a primary screening of the titles and abstracts. Finally, eight eligible articles with 23 records, 329 patients, and 277 controls were included in our meta-analysis. The characteristics of the included studies are presented in Table 1.

Quality Assessment of the Articles

The QUADAS-2 study quality assessments are shown in Fig. 1–2. Most articles included in the current meta-analysis satisfied most of the items in the QUADAS-2 guidelines, which suggests that the overall quality of the included studies was moderate to high.

Diagnostic Accuracy of the Serum miRNAs

The data calculated based on the bivariate model are as follows: the pooled sensitivity was 0.86 (95% CI 0.79–0.90); the pooled specificity was 0.88 (95% CI 0.80–0.93) (Fig. 3–5); the pooled likelihood ratio (PLR) was 7.05 (95% CI 4.20–1.84); the pooled negative likelihood ratio (NLR) was 0.16 (95% CI 11–0.24) (Fig. 3–5); the pooled diagnostic odds ratio (DOR) was 43.46 (95% CI 19.36–97.57) (Fig. 3–5). In addition, the summary receiver operating characteristic (SROC) curve was plotted, and the area under the fitted curve (AUC) was 0.93, which suggests an outstanding diagnostic accuracy of the overall miRNAs (Fig. 6).

Most of the research fell in the middle area, and several studies fell outside, as evaluated by a two-variable box plot (Fig. 7). The I [2] values of the sensitivity and specificity were 82.43 and 86.46, respectively (Fig. 3–5). All the above findings demonstrate significant heterogeneity among the studies.

In addition, the Spearman correlation coefficient was −0.230 ($p = 0.302$), with no evidence of a threshold effect. After eliminating the heterogeneity caused by the threshold effect, a sensitivity analysis was performed. As shown, the goodness-of-fit and the bivariate normality indicated that the bivariate model was suitable for this study. The impact analysis showed that the Cook's distances of record nos. 6, 9, and 12 were all greater than 1, which indicates that these studies were the most dominant studies in weight, and record no. 6 ranked first. Anomaly testing demonstrated that record no. 6 was an outlier and was likely to be the main reason for heterogeneity (Figs. 8 and 9). After eliminating record no. 6, the I [2] values of sensitivity and specificity were reduced by 4.14% and 2.25%, respectively (Fig. 10). To further explore the reason for heterogeneity, a subgroup analysis and meta-regression were performed. The results showed that racial differences, individual miRNAs, test group samples, and fasting status had an impact on sensitivity, which was homogeneous in a certain subgroup. Furthermore, the sample size, whether blood samples were collected during the proliferative phase and whether the study was prospective had impacts on the sensitivity, which was statistically significant. The sample size and whether the test was prospective or retrospective had an impact on specificity (Fig. 9). The results of the statistical

Table 1 Characteristics of eligible studies

No.	Author	Year	Country	mirRAN	Number of patients	Number of controls	TP	FP	FN	TN	Sensitivity (%)	Specific (%)
1	SiHyun Cho [20]	2015	USA	Let-7d	24	24	20	0	4	24	83.30	100
2	Shuang-zheng Jia [21]	2012	China	miR-17-5p	23	23	16	7	7	16	70	70
3	Shuang-zheng Jia [21]	2012	China	miR-20a	23	23	14	2	9	21	60	90
4	Shuang-zheng Jia [21]	2012	China	miR-22	23	23	21	4	2	19	90	80
5	Ahmed M. Maged [22]	2017	Egypt	miR-122	45	35	43	3	2	32	95.6	91.40
6	Ahmed M. Maged [22]	2017	Egypt	miR-199a	45	35	45	0	0	35	100	100
7	WarrenB Nothnick [23]	2016	USA	miR-415a	41	40	35	6	6	34	85.37	84.62
8	Emine Cosar [24]	2016	USA	miR-125-5p	24	24	24	1	0	23	100	96
9	Emin Cosar [24]	2016	USA	miR125b-5p + miR451a + R3613–5p	24	24	24	0	0	24	100	100
10	Petra Pateisky [25]	2018	Austria	miR-154-5p	51	41	34	13	17	28	67	68
11	Kadri Rekker [18]	2015	Spain	miR-200a	61	65	55	25	6	40	90.60	62.50
12	Kadri Rekker [18]	2015	Spain	miR-200b	61	65	55	35	6	30	90.60	45.80
13	Kadri Rekker [18]	2015	Spain	miR-141	61	65	44	19	17	46	71.90	70.80
14	Kadri Rekker [18]	2015	Spain	miR141 + miR20a + miR200b	61	65	51	22	10	43	84.40	66.70
15	Wen-Tao Wang [26]	2013	China	miR-145	60	25	42	1	18	24	70.00	96.00
16	Wen-Tao Wang [26]	2013	China	miR-199a	60	25	47	6	13	19	78.33	76.00
17	Wen-Tao Wang [26]	2013	China	miR-122	60	25	48	6	12	19	80.00	76.00
18	Wen-Tao Wang [26]	2013	China	miR-542-3p	60	25	48	2	18	23	79.6	92.00
19	Wen-Tao Wang [26]	2013	China	miR-141	60	25	43	1	17	24	71.69	96.00
20	Wen-Tao Wang [26]	2013	China	miR-9	60	25	41	1	19	24	68.33	96.00
21	Wen-Tao Wang [26]	2013	China	miR-199a + miR-122 + miR-542-3p + miR-145	60	25	56	1	4	24	93.22	96.00
22	Wen-Tao Wang [26]	2013	China	miR-199a + miR-122 + miR-542-3p	60	25	58	3	2	22	96.61	88.00
23	Wen-Tao Wang [26]	2013	China	miR-199a + miR-122	60	25	48	5	12	20	80.00	80.00

TP true positive, *FP* false positive, *TN* true negative, *FN* false negative

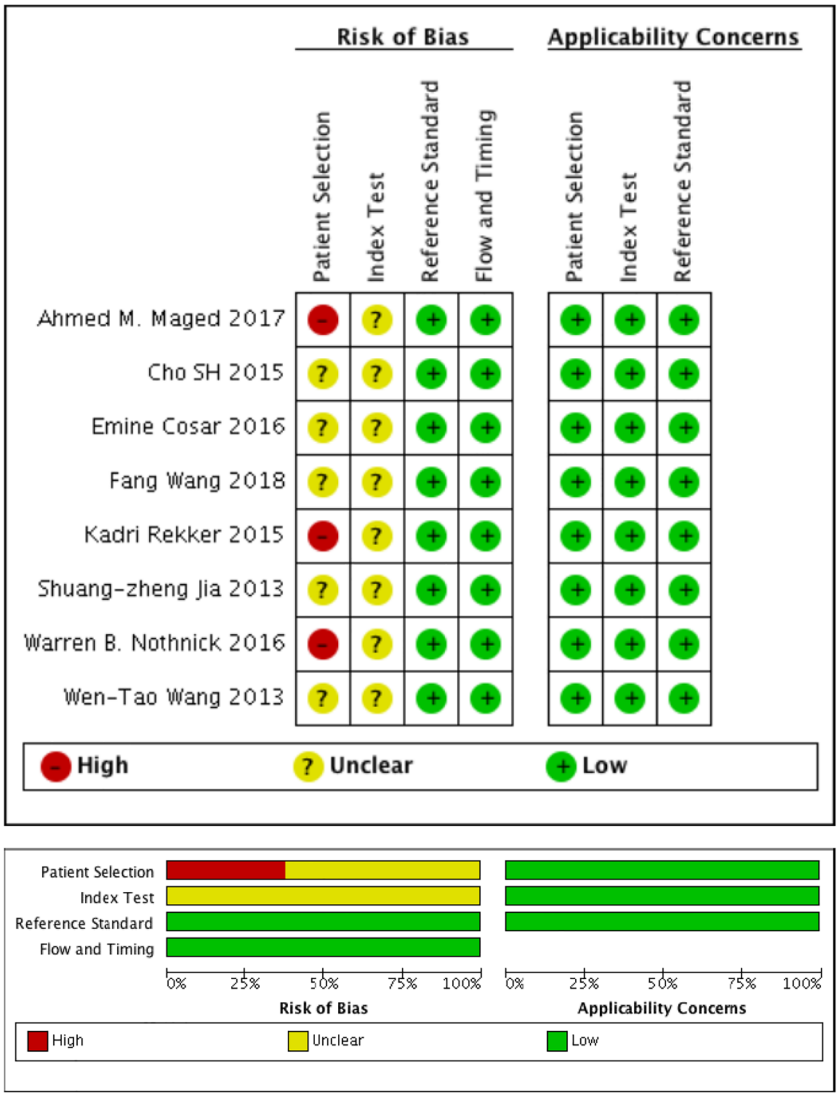
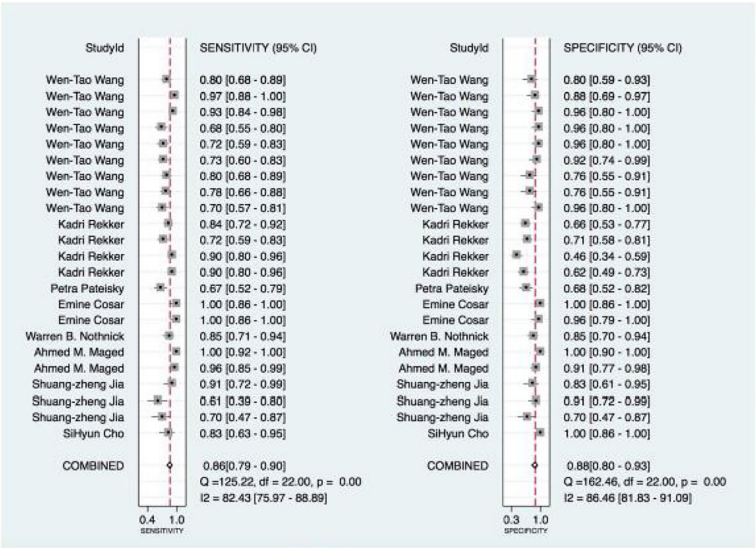


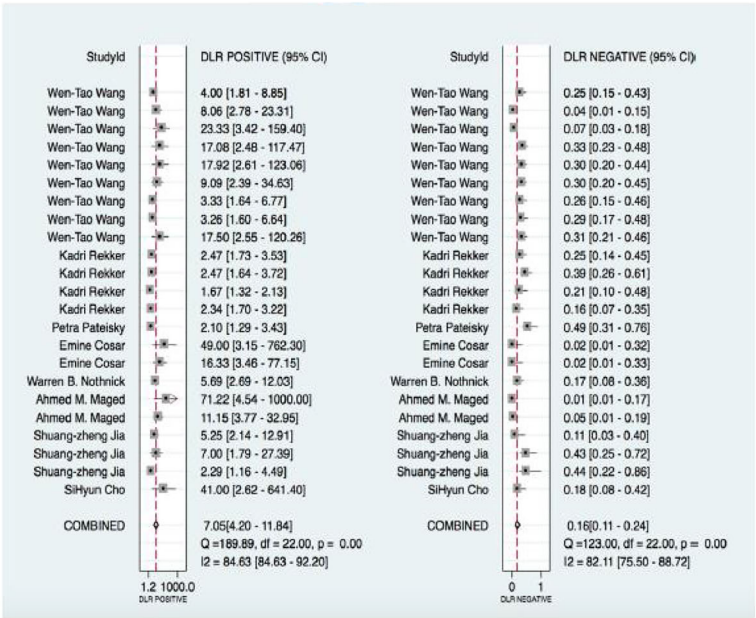
Fig. 1–2 Details of QUADAS-2 quality assessment of each included study (QUADAS-2 tool)

analyses are shown in Table 2. Moreover, Deek's funnel plot revealed no publication bias in the meta-analysis ($p = 0.04$) (Fig. 11).

Discussion

Endometrial tissue that has migrated outside the uterus changes periodically with the fluctuation of ovarian hormones. Recurrent hemorrhage and slow absorption cause proliferation and adhesion of surrounding fibrous tissue. According to site differences, the condition can be divided into two groups: endopelvic and extrapelvic manifestations [27]. Most lesions occur in the pelvic cavity, a condition known as pelvic endometriosis, which often occurs on the ovary, in the peritoneum and in the recto-vaginal pouch. Extrapelvic locations include abdominal wall scars, the ureter, the bladder, the nasal mucosa, and other sites [27–31]. Due to the variety of locations and symptoms, the diagnosis can be difficult, which leads to a delay in treatment. Presently, the diagnosis of endometriosis mainly depends on the following methods: blood markers (e.g., CA-125, NLR) [32, 33], urinary markers (e.g., NNE, VDBP, urine peptide, CK19) [34], pelvic examination (e.g., pelvic tenderness, pelvic mass), clinical symptoms (e.g., continuous aggravation of dysmenorrhea, dyspareunia, chronic pelvic pain, infertility) [35], imaging examination (e.g., pelvic ultrasound and MRI) [36–41], and surgery (e.g., laparoscopic examination, laparoscopic surgery, and laparotomy) [42]. Vaginal ultrasound and abdominal ultrasound are important tools that are used to identify chocolate cysts of the ovary and rectal-vaginal septum lesions, and their sensitivity and specificity are above 90% [43, 44]. However, in some cases, ultrasound





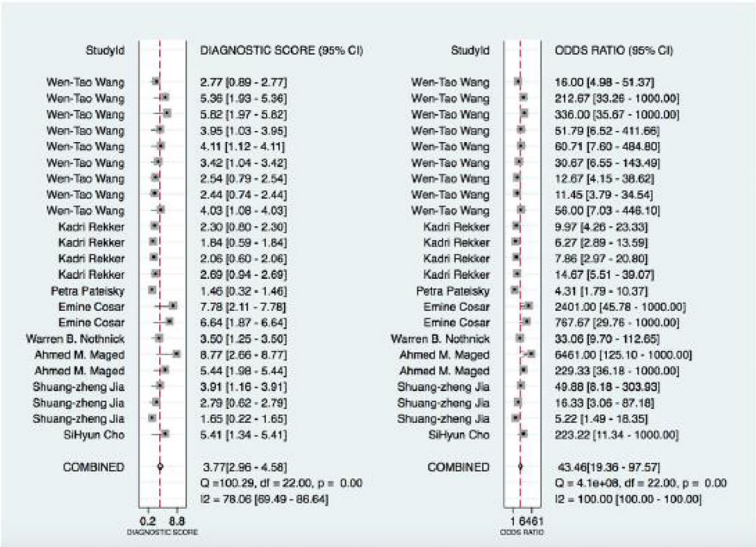


Fig. 3–5 Forest plots for studies on overall microRNAs (miRNAs) used in the diagnosis of endometriosis among 23 records included in the present meta-analysis

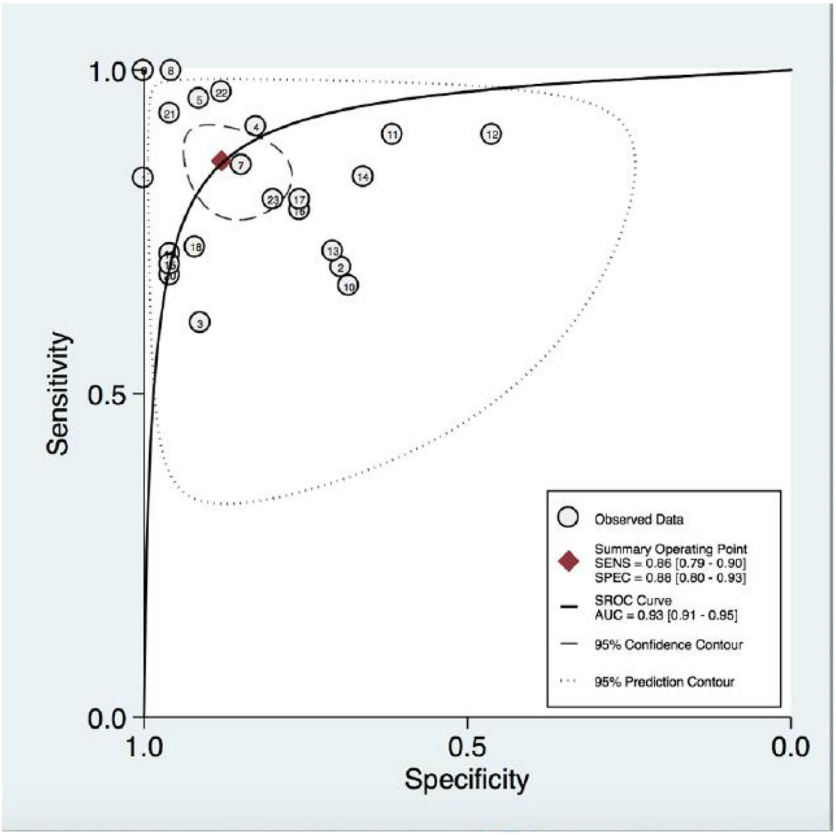


Fig. 6 Summary receiver operator characteristic (SROC) curves based on miRNAs detected in blood samples. AUC area under the curve, SENS sensitivity, SPEC specificity

examinations may not reveal positive findings, such as mild to moderate lesions, minimally changed ovarian endometriosis, infertility and chronic pelvic pain likely caused by endometriosis, sexual pain likely caused by endometriosis, or nodules causing pelvic tenderness [45]. The diagnosis for these early and atypical patients may be

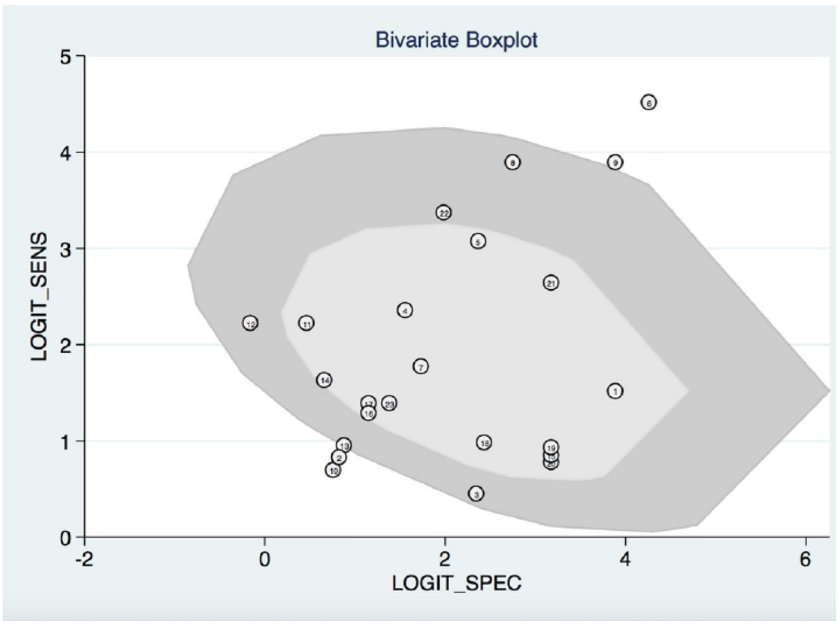


Fig. 7 Bivariate boxplot showed the existence of heterogeneity

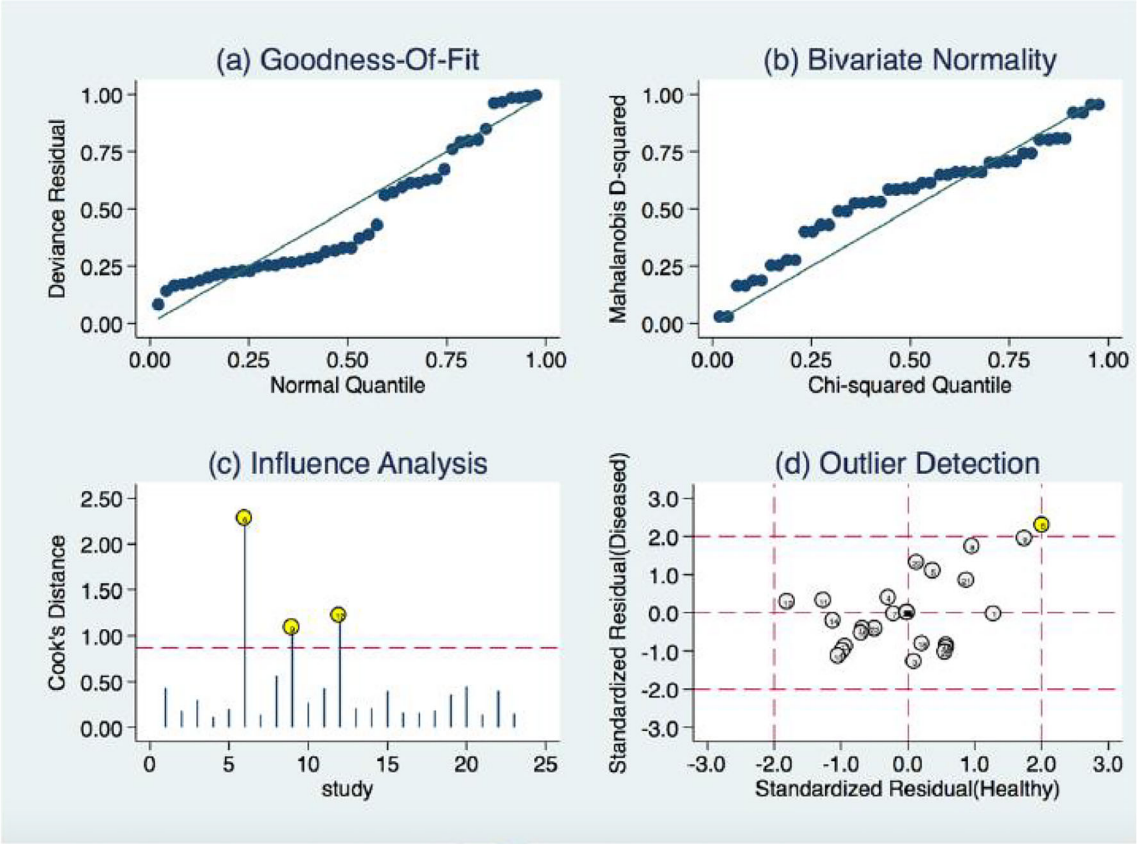


Fig. 8 Diagram of (a) goodness-of-fit, (b) bivariate normality, (C). influence analysis, and (d) outlier detection. Goodness-of-fit and bivariate normality showed that random effects bivariate model is suitable. Influence analysis identified that studies of record nos.6, 9, and 12 were most dominant studies in weight. Outlier detection showed that record no. 6 may be the reason heterogeneity

missed, which results in an increasing severity of the condition. Until the typical symptoms are diagnosed via ultrasound, the patient experiences fertility issues and pain [46]. Therefore, the use of circulating miRNAs as noninvasive serum markers can increase the rate of diagnosis. Early diagnosis and early intervention are therefore crucial to improve female fertility, reduce pain, and improve quality of life.

In recent years, with the development of evidence-based medicine, meta-analyses have been widely applied in the field of medicine. The greatest advantage of a meta-analysis is that it can include homogeneity tests and quantitative merger analyses on multiple similar studies to improve the demonstrated benefits of preliminary conclusions [47, 48]. A meta-analysis is cheaper and even more feasible than large-scale clinical trials and therefore plays an important role in disease analysis, treatment, risk assessment, interventions, preventive measures, and health decision-making. This study had strict literature inclusion and exclusion criteria. After a quality evaluation, it was found that all the included documents were of medium to high quality, which establishes a solid foundation for the reliability of further data analysis. The accuracy of the diagnostic tests was evaluated by plotting the SROC curve followed by the AUC was calculated. The closer the AUC value is to 1, the better the diagnostic assay functions. The AUC in this study was 0.93, which indicates that miRNAs have excellent diagnostic value for endometriosis [49, 50].

We also focused on clinical applicability. In evidence-based medicine, likelihood ratios are used for assessing the value of performing a diagnostic test, and the sensitivity and specificity of the tests are used to determine whether a test result usefully changes the probability that a condition (such as a disease state) exists. The PLR of 7.05 and the NLR of 0.16 (Fig. 4) indicated that patients with endometriosis have a 7.05-fold higher chance of testing positive based on the circulating miRNAs than the controls, and 16% of individuals with endometriosis will have a negative result. Although a DOR of 1 suggests that miRNAs failed to differentiate between endometriosis and control cases, the DOR of 43.46 in our study showed that miRNAs are outstanding diagnostic biomarkers for endometriosis (Fig. 5). We also generated likelihood ratio plots to help determine the clinical applicability of the miRNA

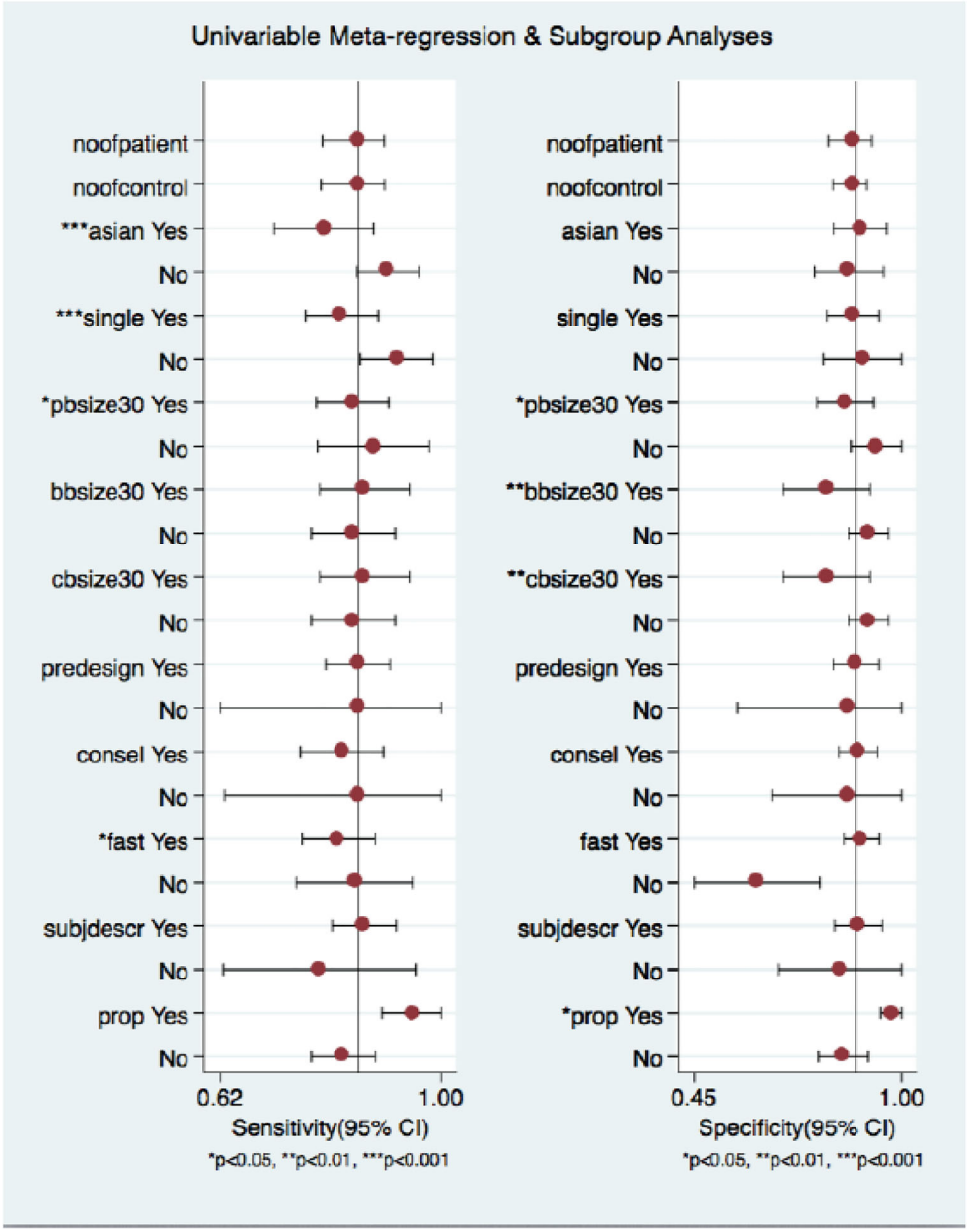


Fig. 9 Univariable meta-regression and subgroup analyses for sensitivity and specificity of miRNAs for diagnosis of endometriosis. Pbsize30, the sample size of patient group was bigger than 30. Cbsize30, the sample size of control group was bigger than 30. Bbsize 30, the sample size of patients and control groups were bigger than 30. Predesign, prospective study. Fulverif, verification of all by same method. Consel, consecutive selection of subjects. Fast, prior fasting of at least 6 h. Subjdescr, adequate description of study subjects. Prop, blood samples were collected during proliferative phase

test (Figs. 12 and 13). A PLR > 10 and an NLR < 0.1 indicate high diagnostic accuracy. The summary point in this paper falls in the lower right quadrant. Based on the current research, the clinical value of miRNA for endometriosis is still limited, and further research is needed. We found that the miRNAs of record nos. 5, 6, 8, 9, and 21 had high diagnostic accuracy and clinical applicability. From the Fagan's nomogram, we found that, when a pre-test probability of 50% was specified, the post-test probability of positivity increased to 88% with a positive likelihood ratio of 7, and the post-test probability of negativity decreased to 14% with a negative likelihood ratio was 0.16 (Fig. 12). These outcomes suggest a stable value of circulating miRNAs in the diagnosis of endometriosis.

This study also has some limitations. In this investigation, significant heterogeneity was observed. Subgroup and sensitivity analyses were performed, but the results only partially explained the causes of the heterogeneity. The cutoff values are different in the included studies,

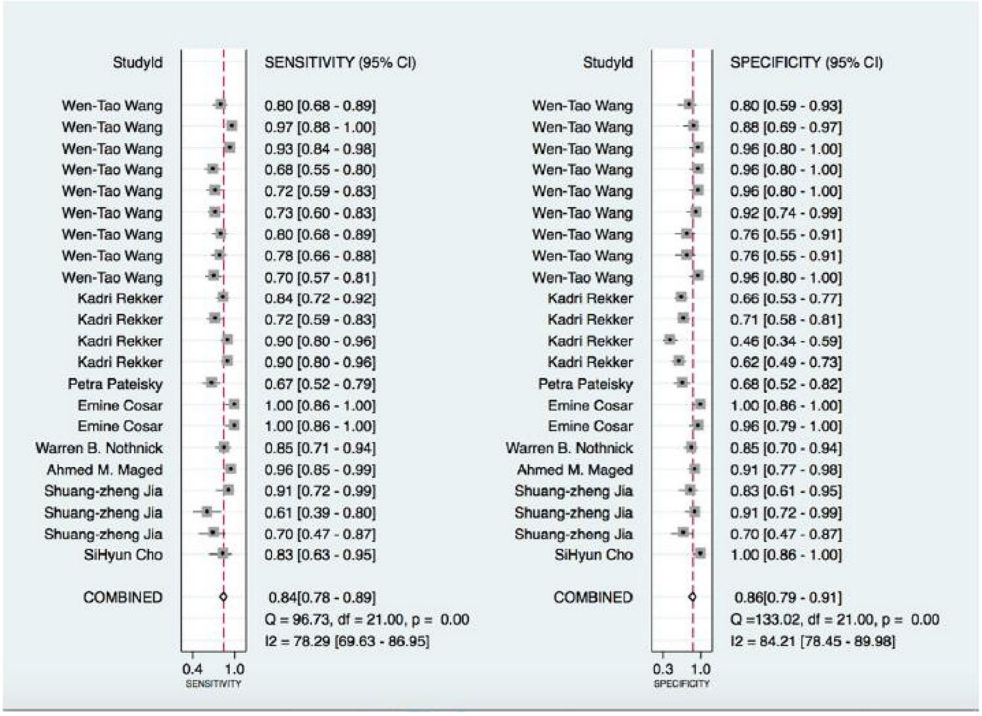


Fig. 10 Forest plots for studies on overall miRNAs used in the diagnosis of endometriosis among records (outlier record was excluded)

which may be one of the reasons for heterogeneity. Moreover, studies with positive results are easier to publish than those with negative results, which may exaggerate the accuracy of the overall diagnosis. In addition, we included only literature published in English, which may have affected the research results.

Materials and Methods

Study Protocol

The research protocol was drafted at the beginning of this project according to the Cochrane Collaboration format [51].

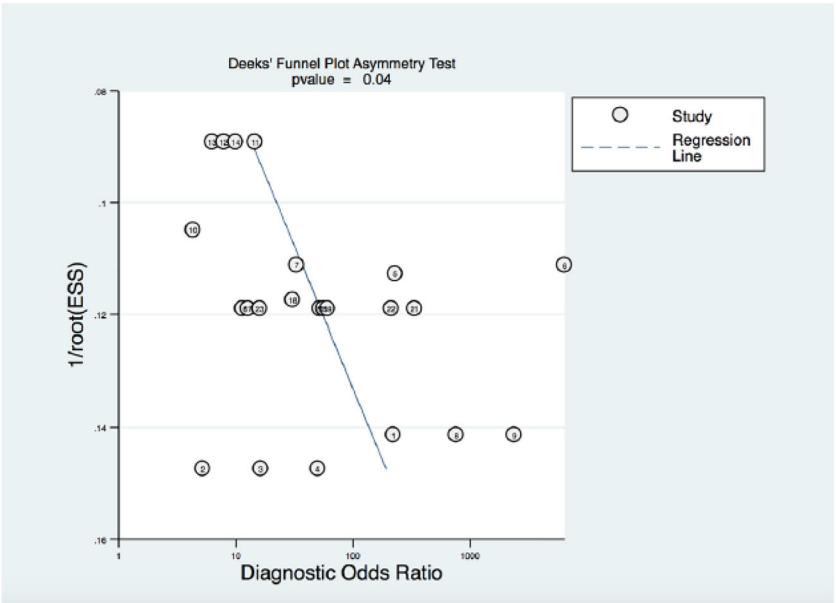


Fig. 11 Deek's funnel plot indicates no significant publication bias ($p = 0.04 < 0.1$)

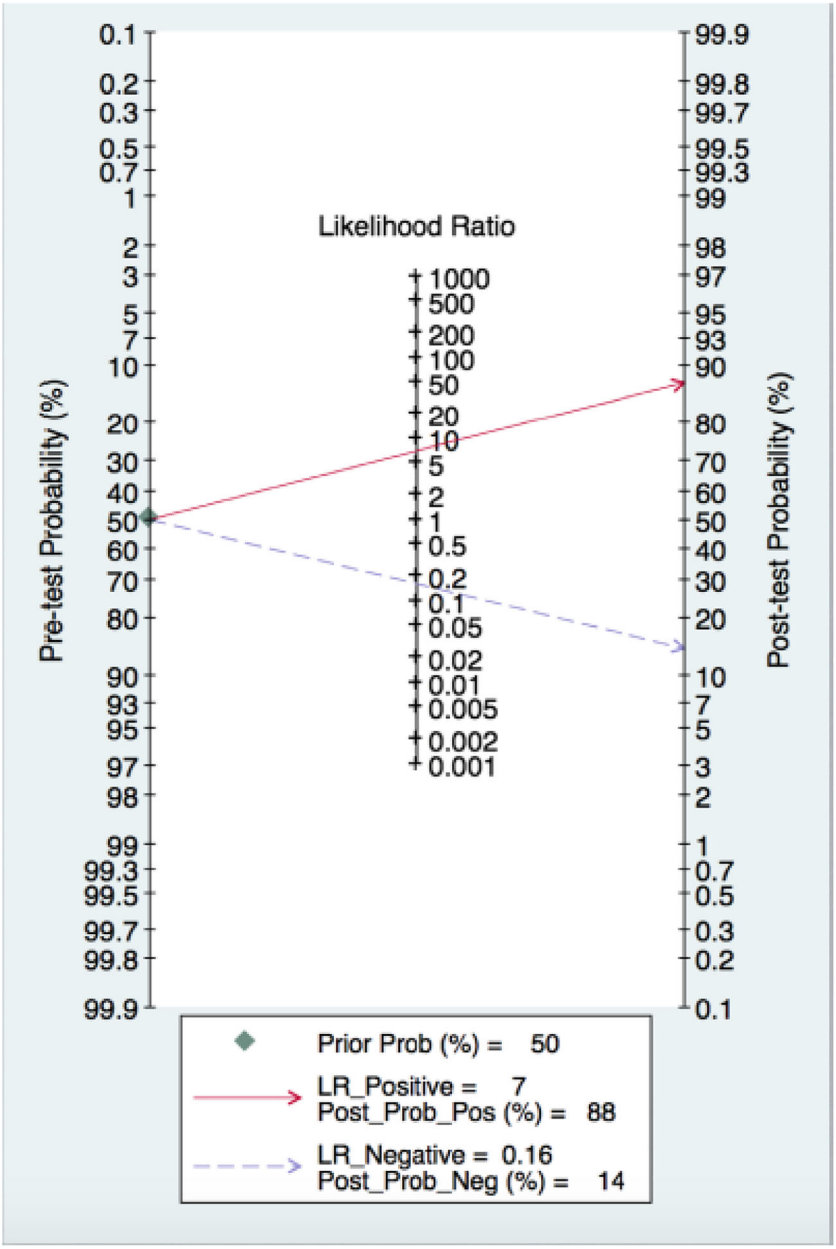


Fig. 12 Fagan's nomogram for calculation of post-test probabilities

Search Strategy and Study Selection

A comprehensive search was performed to identify all studies that assessed the diagnostic accuracy of plasma- or serum-based miRNAs for endometriosis; PubMed, EMBASE, and Cochrane Library were searched up to June 1, 2018. Keywords included the following: "plasma" or "serum" or "blood," "miRNA," "endometriosis," and "biomarker." Both Medical Subject Headings (MeSH) and freestyle words were used as search terms. The reference lists of relevant studies and reviews were also searched for potentially eligible studies. (For details, see the supplemental material.)

The Criteria and Screening Process

The inclusion criteria for the primary studies were as follows: (1) the study was a diagnostic study of serum miRNAs; (2) the subjects included endometriosis patients and control groups; (3) all patients with endometriosis were diagnosed by the gold standard method (laparoscopic exam); and (4) sufficient information was available to

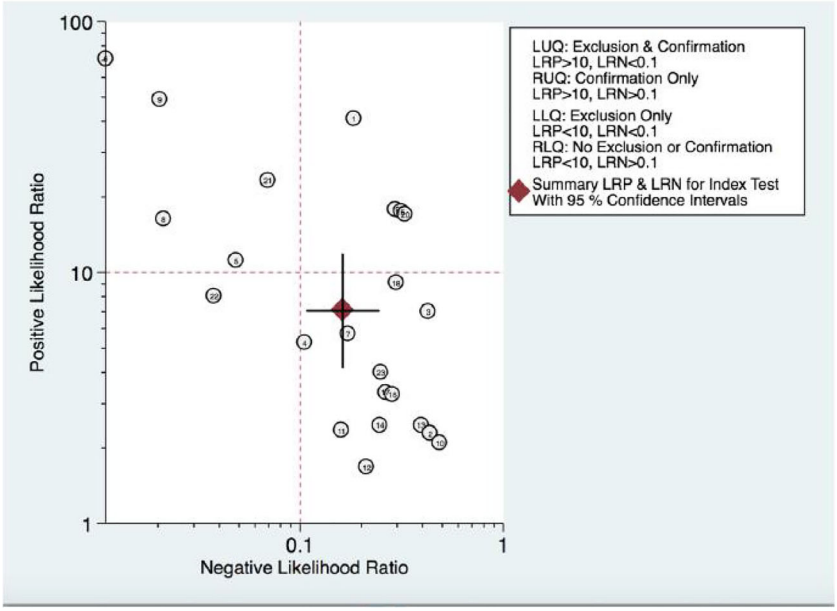


Fig. 13 Assessment of the clinical applicability of microRNAs (miRNAs) for diagnosis. Summary of positive likelihood ratio and negative likelihood ratio for diagnosis of endometriosis. LRN likelihood ratio negative, LRP likelihood ratio positive, LLQ left lower quadrant, LUQ left upper quadrant, RLQ right lower quadrant, RUQ right upper quadrant

Table 2 Statistical results of meta-regression

Parameter	Category	LRTChi2	*p* value	I^2	I^2 low	I^2 high
No. of patients		3.64	0.16	45	0	100
No. of control		14.24	0.00	86	71	100
Asian	Yes	6.71	0.03	70	34	100
	No	.	.	.	.	.
Single	Yes	3.22	0.20	38	0	100
	No	.	.	.	.	.
Pbsize30	Yes	2.15	0.34	7	0	100
	No	.	.	.	.	.
Bbsize30	Yes	4.48	0.11	55	0	100
	No	.	.	.	.	.
Cbsize30	Yes	4.48	0.11	55	0	100
	No	.	.	.	.	.
Predesign	Yes	0.03	0.99	0	0	100
	No	.	.	.	.	.
Consel	Yes	90.83	0.00	98	96	99
	No	.	.	.	.	.
Fast	Yes	43.62	0.00	95	92	99
	No	.	.	.	.	.
Subjdescr	Yes	1.02	0.60	0	0	100
	No	.	.	.	.	.
Prop	Yes	9.13	0.01	78	52	100
	No	.	.	.	.	.

Pbsize30 the sample size of patient group were bigger than 30, *Cbsize30* the sample size of control group were bigger than 30, *Bbsize30* the sample size of patients and control groups were bigger than 30, *Predesign* prospective study, *Fulverif* verification of all by same method, *Consel* consecutive selection of subjects, *Fast* prior fasting of at least 6 h, *Subjdescr* adequate description of study subjects, *Prop* blood samples were collected during proliferative phase

construct 2 × 2 tables that consisted of true positives (TPs), false positives (FPs), true negatives (TNs), and false negatives (FNs). Articles were excluded based on the following criteria: (1) written in a language other than English; (2) not conducted in humans; (3) reviews, letters, and meeting records; (4) studies with insufficient data. The studies included in our meta-analysis were independently assessed by two investigators. All the selected studies were managed using EndNote X9.

We used a search strategy to retrieve the target documents from the database. We eliminated duplicate articles and then removed noncompliant documents by title, abstract, and full-text screening.

Data Extraction and Quality Assessment

The following data were extracted: first author's name, year and country of publication, number of patients and number of controls, miRNA type being tested, and specificity and sensitivity values of the tested miRNAs. QUADAS-2 guidelines were used to evaluate the quality of the included studies. The quality assessment was managed by Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark).

Data Analysis

We extracted TP, FP, FN, and TN values from each study and calculated the pooled sensitivity, specificity, PLR, NLR, DOR, and 95% confidence intervals. The diagnostic value of miRNAs was assessed by plotting the SROC curve and its AUC. Deeks' funnel plot was used to evaluate the publication bias. Chi-squared and I^2 tests were used to assess heterogeneity between studies. If $p < 0.1$ or $I^2 > 50\%$, the heterogeneity was considered significant between studies. If heterogeneity existed, meta-regression, subgroup, and sensitivity analyses were designed to explore the sources of heterogeneity. In addition, the Spearman correlation coefficient was calculated to determine whether the heterogeneity in the meta-analysis was related to the threshold effect; when $p > 0.05$, there was no threshold effect. The data analyses were performed using Meta-Disc statistical software version 1.4 (XI Cochrane Colloquium, Barcelona, Spain) and STATA software (version 14.0, StataCorp, MIDAS module).

Conclusions

Taken together, our research findings suggest that circulating miRNAs are potential noninvasive diagnostic biomarkers for endometriosis. In regard to clinical applicability, large-scale, high-quality prospective, and retrospective studies should be conducted to further explore the clinical value of circulating miRNAs for endometriosis. The subgroup analysis suggests that multiple miRNA combinations may be more accurate than individual miRNAs in distinguishing individuals with and without endometriosis. Finally, the results may be affected by a patient's menstrual cycle.

Author Contributions Conceptualization, Ling Zhou; methodology, Ling Zhou; software, Ling Zhou; validation, Ling Zhou and Yan Cheng; formal analysis, Ling Zhou; investigation, Ling Zhou and Yan Cheng; resources, Ling Zhou and Jianhua Gao; data curation, Ling Zhou and Yan Chen; writing—original draft preparation, Ling Zhou; writing—review and editing, Ling Zhou and Shankar Sandhya; supervision, Jianhua Gao; project administration, Guangmei Zhang.

Funding Information This work was supported by the National Natural Science Foundation of China (No. 81772780).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Brosens I, Benagiano GJIJMR. Endometriosis, a modern syndrome. Indian J Med Res. 2011;133(6):581–93.
2. Vercellini P, Viganò P, Somigliana E, Fedele LJNRE. Endometriosis: Pathogenesis and Treatment. Nat Rev Endocrinol. 2014;10(5):261–75.
3. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. JAoG, Obstetrics. 2009;280(4):529–38.
4. Fuldeore MJ, Soliman AMJG, Investigation O. Prevalence and symptomatic burden of diagnosed endometriosis in the United States: national estimates from a cross-sectional survey of 59,411 women. 2016;82(5).
5. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. 2011;96(2):366–373.e368.
6. Sheveleva T, Bejenar V, Komlichenko E, Dedul A, Malushko AJGE. Innovative approach in assessing the role of neurogenesis, angiogenesis, and lymphangiogenesis in the pathogenesis of external genital endometriosis. 2016;32(sup2):75–79.
7. Scully REJEHP. Classification of human ovarian tumors. 1987;73(73):15–24.
8. Marí-Alexandre J, García-Oms J, Barceló-Molina M, et al. microRNAs and angiogenesis in endometriosis. 2015;135:S38-S40.
9. Gadducci A, Lanfredini N, Tana R. Novel insights on the malignant transformation of endometriosis into ovarian carcinoma 2014;30(9):612–617.
10. Nisenblat V, Bossuyt PMM, Shaikh R, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;5.
11. Mehedintu C, Plotogea MN, Ionescu S, Antonovici M. Endometriosis still a challenge. J Med Life. 2014;7(3):349–57.
12. Wang J, Chen J, Sen S. MicroRNA as Biomarkers and Diagnostics. J Cell Physiol. 2016;231(1):25–30.
13. Maríalexandre J, Sánchezizquierdo D, Gilabertestellés J, Barcelómolina M, Brazaboïls A, Sandoval JJIJoMS. miRNAs Regulation and its role as biomarkers in endometriosis. 2016;17(1):93.

14. Nothnick WBJSiRM. MicroRNAs and endometriosis: distinguishing drivers from passengers in disease Pathogenesis. 2017;35(02):173–180.
15. Haikalis ME, Wessels JM, Leyland NA, Agarwal SK, Foster WGJBoR. miRNA expression pattern differs depending on endometriosis lesion type. 2018.
16. Burney RO, Hamilton AE, Aghajanova L, et al. MicroRNA expression profiling of eutopic secretory endometrium in women with versus without endometriosis 2009;15(10):625–631.
17. Liang Z, Chen Y, Zhao Y. miR-200c suppresses endometriosis by targeting MALAT1 in vitro and in vivo. Stem Cell Research & Therapy 2017;8(1):251.
18. Rekker K, Saare M, Roost AM, et al. Circulating miR-200–family micro-RNAs have altered plasma levels in patients with endometriosis and vary with blood collection time. Fertil Steril. 2015;104(4): 938–946.e932.
19. Seifer BJ, Su D, Taylor HS. Circulating miRNAs in murine experimental endometriosis: decreased abundance of let-7a. 2016;24(3): 376.
20. Cho SH, Mutlu L, Grechukhina O, Taylor HSJF, Sterility. Circulating microRNAs as potential biomarkers for endometriosis. 2015;103(5):1252–1260.e1251.
21. Shuang-Zheng J, Yunpeng Y, Jinghe L, Pengran S, Jinhua LJHR. Plasma miR-17-5p, miR-20a and miR-22 are down-regulated in women with endometriosis. 2013;28(2):322–330.
22. Maged AM, Deeb WS, El AA, et al. Diagnostic accuracy of serum miR-122 and miR-199a in women with endometriosis. 2017;141(1).
23. Nothnick WB, Falcone T, Joshi N, Fazleabas AT, Graham AJRS. Serum miR-451a levels are significantly elevated in women with endometriosis and recapitulated in baboons (Papio anubis) with experimentally-induced disease. 2016;24(8):1195.
24. Cosar E, Mamillapalli R, Ersoy GS, Cho S, Seifer B, Taylor HS. Serum microRNAs as diagnostic markers of endometriosis: a comprehensive array-based analysis. Fertil Steril. 2016;106(2):402–9.
25. Pateisky P, Pils D, Szabo L, et al. hsa-miRNA-154-5p expression in plasma of endometriosis patients is a potential diagnostic marker for the disease. 2018.
26. Wang WT, Zhao YN, Han BW, Hong SJ, Chen YQ. Circulating microRNAs identified in a genome-wide serum microRNA expression analysis as noninvasive biomarkers for endometriosis. J Clin Endocrinol Metab. 2013;98(1):281–9.
27. Sonavane SK, Kantawala KP, Menias CO. Beyond the boundaries-endometriosis: typical and atypical locations. Curr Probl Diagn Radiol. 2011;40(6):219–32.
28. Ahn SH, Singh V, Tayade C. Biomarkers in endometriosis: challenges and opportunities. Fertil Steril. 2017;107(3):523–32.
29. Machairiotis N, Stylianaki A, Dryllis G, et al. Extrapelvic endometriosis: a rare entity or an under diagnosed condition? Diagn Pathol. 2013;8:194.
30. Punnonen R, Klemi PJ, Nikkanen V. Postmenopausal endometriosis. Eur J Obstet Gynecol Reprod Biol. 1980;11(3):195–200.
31. Balleyguier C, Chapron C, Chopin N, Helenon O, Menu Y. Abdominal wall and surgical scar endometriosis: results of magnetic resonance imaging. Gynecol Obstet Investig. 2003;55(4):220–4.
32. May KE, Conduit-Hulbert SA, Villar J, Kirtley S, Kennedy SH, Becker CM. Peripheral biomarkers of endometriosis: a systematic review. Hum Reprod Update. 2010;16(6):651–74.
33. Kim SK, Park JY, Jee BC, Suh CS, Kim SH. Association of the neutrophil-to-lymphocyte ratio and CA 125 with the endometriosis score. Clin Exp Reprod Med. 2014;41(4):151–7.
34. El-Kasti MM, Wright C, Fye HK, Roseman F, Kessler BM, Becker CM. Urinary peptide profiling identifies a panel of putative biomarkers for diagnosing and staging endometriosis. Fertil Steril. 2011;95(4):1261–1266.e1-6.
35. Tanbo T, Fedorcsak P. Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options. Acta Obstet Gynecol Scand. 2017;96(6):659–67.
36. Exacoustos C, Zupi E, Piccione E. Ultrasound imaging for ovarian and deep infiltrating endometriosis. Semin Reprod Med. 2017;35(1):5–24.
37. Reid S, Condous G. Update on the ultrasound diagnosis of deep pelvic endometriosis. Eur J Obstet Gynecol Reprod Biol. 2017;209: 50–4.
38. Hoyos LR, Johnson S, Puscheck E. Endometriosis and imaging. Clin Obstet Gynecol. 2017;60(3):503–16.
39. Thalluri AL, Knox S, Nguyen T. MRI findings in deep infiltrating endometriosis: a pictorial essay. J Med Imaging Radiat Oncol. 2017;61(6):767–73.
40. Bazot M, Darai E. Diagnosis of deep endometriosis: clinical examination, ultrasonography, magnetic resonance imaging, and other techniques. Fertil Steril. 2017;108(6):886–94.
41. Fassbender A, Burney RO, O DF D'HT, Giudice L. Update on biomarkers for the detection of endometriosis. 2015;2015: 130854–Biomed Res Int.
42. Gupta D, Hull ML, Fraser I, et al. Endometrial biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;(4):Cd012165.
43. Guerriero S, Ajossa S, Minguez JA, et al. Accuracy of transvaginal ultrasound for diagnosis of deep endometriosis in uterosacral ligaments, rectovaginal septum, vagina and bladder: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015;46(5):534–45.
44. Guerriero S, Ajossa S, Orozco R, et al. Accuracy of transvaginal ultrasound for diagnosis of deep endometriosis in the rectosigmoid: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2016;47(3):281–9.
45. Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2014;28(5):655–81.
46. Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of endometriosis on women's lives: a qualitative study. BMC Womens Health. 2014;14:123.
47. Dawson DV, Pihlstrom BL, Blanchette DR. Understanding and evaluating meta-analysis. J Am Dent Assoc. 2016;147(4):264–70.
48. Noordzij M, Hooft L, Dekker FW, Zoccali C, Jager KJ. Systematic reviews and meta-analyses: when they are useful and when to be careful. Kidney Int. 2009;76(11):1130–6.
49. Harbord Roger WP. Metandi: meta-analysis of diagnostic accuracy using hierarchical logistic regression. Stata J. 2009;9:211–9.
50. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. J Clin Epidemiol 2006;59(12):1331–1332; author reply 1332–1333.
51. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009;339:b2700.