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REVIEW

# Circulating non-coding RNAs as non-invasive diagnostic markers of endometriosis: a comprehensive meta-analysis

Yanhui Li[1,2] · Qionghua Chen[1,2]

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## Abstract

**Background** Circulating non-coding RNAs have great potential for diagnosing endometriosis as non-invasive markers. We have assessed the potential accuracy and utility for diagnosis of endometriosis.

**Methods** We searched many bases to identify the included literature, which included English bases, such as, Pubmed, Embase, Web of Science, Cochrane library and Chinese bases, for instance, CNKI, Wang Fang, VIP, DuXiu, ChaoXing. We also calculated the general sensitivity and specificity, negative likelihood ratio, positive likelihood ratio, diagnostic odds ratio, ROC curve plotting and so on with Stata 15. $I^2$ could test the heterogeneity of the meta-analysis, the funnel plot valuated whether meta-analysis had a publication bias. Regression analysis could explore heterogeneity in studies.

**Result** Comprehensive reading and integrating extracted data, we included 11 published papers. The total number of people included in the case group was 453, and the control group was 362. We, respectively, calculated the general sensitivity and general specificity which were 0.81 (95% CI 0.76–0.85) and 0.77 (95% CI 0.71–0.82) by bivariate analysis. The area under the ROC curve was 0.86 (95% CI 0.83–0.89). There was significant heterogeneity in studies which is $I^2 = 89.62\%$ (95% CI 87.41%–91.83%). In addition, the results of meta-regression and subgroup analysis showed that the heterogeneity might come from gold standard, evaluation standard, experimental group size, experimental sample and race

**Conclusion** The circulating non-coding RNAs have great ability of diagnosing endometriosis as non-invasive markers which were performed robustly and accurately.

**Keywords** Non-coding RNAs · Endometriosis · Biomarkers · Non-invasive and meta

## Background

Endometriosis is a common gynecological disease in women caused by the implantation of active endometrial cells in the ovaries, fallopian tubes and peritoneum [1–3]. Worldwide, it has resulted in 30–40% of women undergoing dysmenorrhea and infertility which places a heavy burden on health care services [4] and carries enormous consequences for societies [5]. Up to now, the laparoscopy is the only one golden standard [6], while, as an invasive method for the diagnosis of endometriosis, it brings about great trauma, huge economic burden and mental stress. Furthermore, the CA125, TNFα and IL-6 are limited due to the lack of diagnostic accuracy. Moreover, incipient symptoms of endometriosis such as dysmenorrhea, chronic pelvic pain, irregular menstruation and infertility are not specific and cannot distinguish it very well from other gynecological diseases. It is also particularly crucial to diagnose endometriosis early in pregnant women. Hence, the increasing infertility ratio of endometriosis on account of delayed diagnosis and treatment prolonged the time of hospitalization and augmented average cost. To solve these problems, it is necessary for us to search an early non-invasive and accurate diagnostic method.

This was achieved not only thanks to the development of a new generation of sequencing technology, but also the push of the Encyclopedia of DNA Elements (ENCODE) and the Functional Annotation of the Mammalian Genome (FANTOM).

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00404-019-05290-x) contains supplementary material, which is available to authorized users.

✉ Qionghua Chen
cqhua616@126.com

[1] Department of First Affiliated Hospital of Xiamen University, Zhenhai Road, Siming District, Xiamen 361000, China

[2] Department of Xiamen University, Xiamen 361000, Fujian Provincial, China

Non-coding RNAs have been increasingly recognized for more than a decade [7, 8]. The circulating non-coding RNAs include microRNA, long non-coding RNA and circRNA, etc. They widely participate in various physiological and pathological processes. MicroRNA are endogenous 20–22 nt non-coding RNAS [9]. They can degrade or block the translation of their target mRNA and usually work as post-DNA transcription regulators for gene expression. Evidence shows that microRNA can be stably tested in circulating plasma and serum [10]. Circulating microRNA had already been used as a biomarker for early preclinical diagnosis including endometriosis [11–13]. Simultaneously, the long non-coding RNA is a molecule with a length of more than 200 nt, which plays an important role in a wide range of disease biology areas [7, 14, 15]. It has few class of molecules. Transcription by RNA polymerase II (RNA PII), polyadenylation and splicing is predominantly localized in the nucleus [16]. It is available for quantitative detection of the non-coding RNAs gene expression in the plasma or serum because of the stability of secondary structures [17, 18]. These characteristics indicate that the non-coding RNAs not only can be a method of non-invasive detection of endometriosis, but also it plays an important role in the development of the disease [19–21]. Some scientific researches have analyzed the long non-coding RNA expression's profile in endometriosis. They also have provided new experimental evidence for the pathogenesis which influences endometrial receptivity.

Although there are only three meta-analyses about non-invasive diagnosis of endometriosis [22, 23], the first one introduced many non-invasive diagnostic markers in 2013. The other two studies described microRNA information, nevertheless, it ignored to extract and analyze the diagnostic data information. The reason we did this meta-analysis was to diagnose endometriosis early in the population in a non-invasive way and to summarize diagnostic criteria information.

## Materials and methods

### Search and selection

We comprehensively searched for studies in Pubmed,Embase, Web of science and Cochrane library in English base, We performed the search using medical subject headings (MeSH): "Endometriosis", "microRNA","lncRNA" and Entry Terms (Synonyms): "Endometrioses", "Endometrioma", "Endometriomas","MicroRNA", "miRNAs", " microRNAs", "miRNA". Meanwhile, we also searched Chinese bases such as CNKI, WangFang database, VIP and DuXiu. In Pubmed, Embase and Web of Science, we also used the search terms "NOT" "comment" OR "letter" OR "editor" OR "animal experiment" OR "meeting summary" OR "lawsuit document" OR "poster" OR "presentation" OR "meta-analysis" OR "case report"). We searched for the current published literature, the references of main research, previous systematic reviews and meta-analyses that were conducted from the past until April 20, 2019. We assessed endometriosis with a uniform gold standard. For a definitive pathologic diagnosis, we used a system modified by the American society for reproductive medicine(ASRM) to determine the extent of endometriosis and the true and false positives included. The names of circulating non-coding RNAs and the sensitivity and specificity of each study must be confirmed. Only if enough information was provided to produce 2 × 2 crosstabs, we would adopt it. We just included English literature and Chinese literature. Studies that were animal experiments, reviews, correspondence, case reports, expert opinions and reviews were eliminated.

### Procedure

Data were extracted and the quality of studies was assessed by two researchers independently. Through consultation of different evaluations, we could reach consensus by consultation. If we could not, it was submitted to a third researcher. Following the methodological characteristics of evidence-based medicine, we extracted data and collected clinical information of the included people and the changes in circulating non-coding RNAs gene expression. The scientificity of the experimental diagnostic method was estimated, as well as the reasonability of the cutoff value setting. Each researcher also recorded the number of true positives and false negatives, sensitivity, specificity and the area under the curve. Because some studies did not have all the information available, we contacted the authors. We had enquired whether they could provide the full text of the literature to us. If we received no reply, we excluded those studies.

We assessed the methodological quality of the study using the diagnostic accuracy study quality assessment checklist (QUADAS-2). QUADAS-2 lists were used for each article and each answer was "yes", "no", "unclear", "low risk", "high risk" or "uncertain". A bivariate random effects model tested them as the source of variation and bias.

### Statistic analysis

The 2 × 2 tables were listed, it included the number of true positives, false negatives, false positives and true negatives of patients with endometriosis and without endometriosis. The hierarchical summary receiver operation curve for circulating non-coding RNA was constructed, including sensitivity and specificity of the curve and a 95% confidence interval. Evaluation of the quality of the included literature was done by Revman 5. Meanwhile, STATA (version 15) of the MIDAS module bivariate meta-analysis model was applied to our analysis to calculate the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic OR (DOR).

We also established a summary of the subject performance characteristics (SROC) curve and calculated the AUC and 95% CI. The data were validated by the hierarchical SROC (HSROC) model through the STATA (version 15) METANDI module. Heterogeneity of non-threshold effects was assessed using the inconsistency index ($I^2$) test. $I^2$ was calculated to evaluate the heterogeneity of this meta-analysis. If there was significant heterogeneity between studies, the potential sources of heterogeneity were explored by meta-regression. If $I^2$ was greater than 50%, it indicated that there was significant heterogeneity between studies. Meta-regression analysis was further applied to identify potential sources of heterogeneity. Fagan's chart was used to prove pre-probabilities and post-probabilities. Deeks' funnel plot asymmetry assessed potential publication bias.

## Result

A total of 1006 papers were retrieved from database, and 618 papers were adopted by removing duplicate between databases. After reading the title and abstract, we excluded 441 again. Subsequently, after reviewing the full text, we excluded another 400 papers (one animal experiment, three meta-analyses, two conference papers, no significant correlation in 178). Finally, 23 qualified studies were left after the statistical analysis. Subsequently, we included 11 studies and excluded other studies that could not obtain effective information [24–33]. Since multiple circulating non-coding RNAs were reported in several studies about the diagnostic accuracy, we analyzed 50 data sets (Fig. 1).

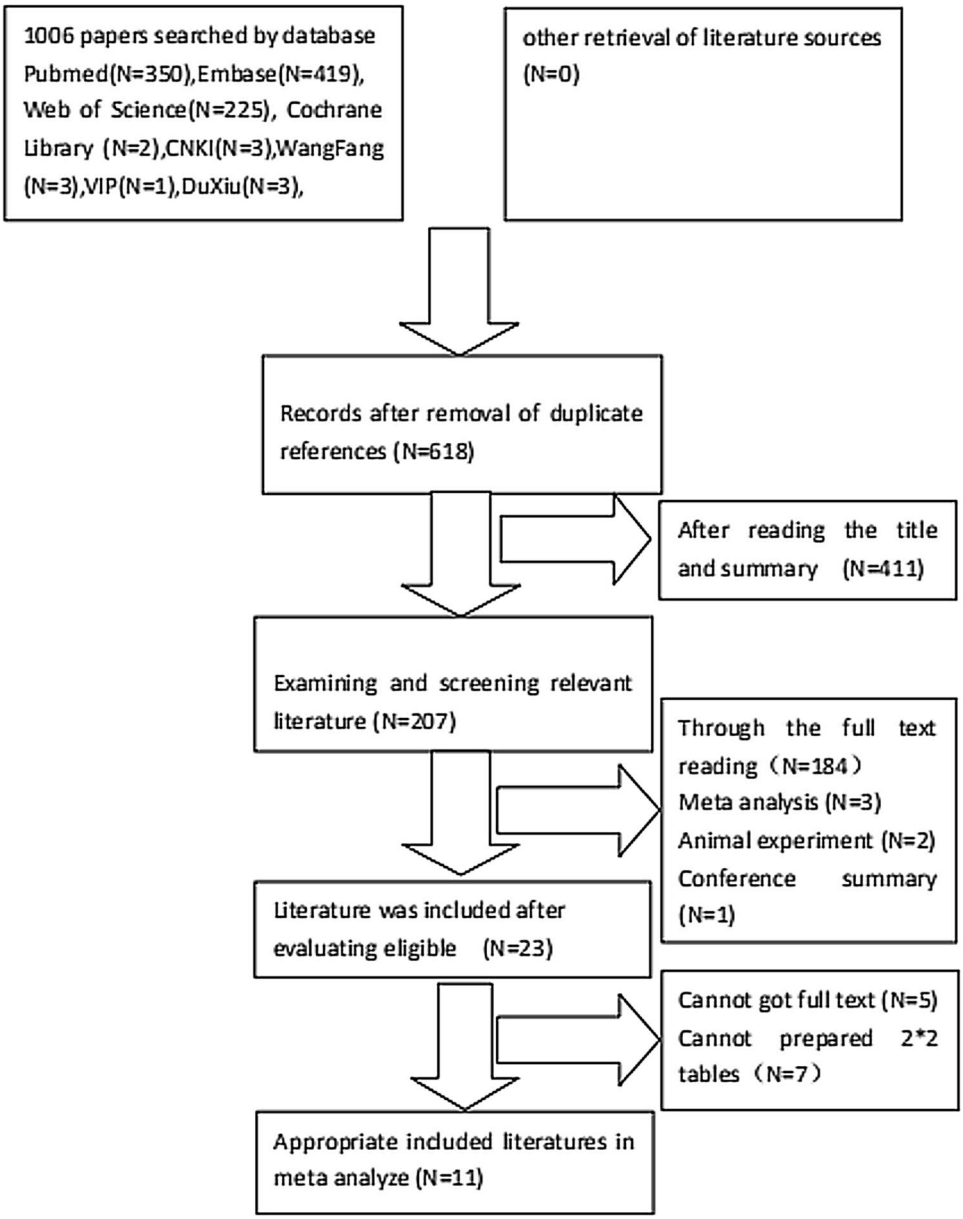



**Fig. 1** The process of literature inclusion

**Table 1** *TP* true positive, *FP* false positive, *FN* false negative, *TN* true negative, *SEN* sensitivity, *SPE* specificity, *AUC* the area under the receiver operating characteristic curve

| First author | Year | Country | Race | Cases/controls | Sample type | Mean age case/controls | Stage of Endometnolsis in cases | Trait control | Normalize | Test method | Cut-off | Study design | Markers studied | Sensitivity | Specificity | AUC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suryavanshi | 2013 | USA | Mixed | 33/20 | Plasma | 38.75/36.2 4 | NA | Non-EMS | U6 | qRT-PCR | NA | Cohort | miR-16<br>miR-191<br>miR-195 | 0.88 | 0.6 | 0.9 |
| | | | | 33/14 | | 38.75/55.3 6 | | EAOC | | | | | miR-21<br>miR-362-5P<br>miR-1274a | 0.57 | 0.91 | 0.92 |
| | | | | 33/21 | | 38.75/65.5 2 | | SOC | | | | | miR-362-5p<br>miR-628-3p<br>miR-1915 | 0.9 | 0.73 | 0.88 |
| 2013 | | China | Asian | 23/23 | Plasma | 34.1/32.1 | 1 II III IV | Mm EMS | miR-16 | qRT–PCR | 0.9057 | Case-control | miR-17-5p | 0.7 | 0.7 | 0.74 |
| | | | | | | | | | | | 0.6879 | | miR-20a | 0.6 | 0.9 | 0.79 |
| | | | | | | | | | | | 0.5647 | | miR-22 | 0.9 | 0.8 | 0.85 |
| Wang | 2013 | China | Asian | 24/24 | Serum | 20.65/20.55 | 1 II III IV | Non-EMS | U6 | qRT–PCR | NA | Case-control | miR-145’ | 0.7 | 0.96 | 0.88 |
| | | | | | | | | | | | | | miR-1993 | 0.7833 | 0.76 | 0.83 |
| | | | | | | | | | | | | | miR-122 | 0.8 | 0.76 | 0.84 |
| | | | | | | | | | | | | | miR-542-3p | 0.7966 | 0.92 | 0.85 |
| | | | | | | | | | | | | | miR-141* | 0.7169 | 0.96 | 0.85 |
| | | | | | | | | | | | | | miR-9" | 0.6833 | 0.96 | 0.83 |
| | | | | | | | | | | | 0.4951 | | miR-145*<br>mi R-199a<br>miR-122 | 0.9322 | 0.96 | 0.99 |
| | | | | | | | | | | | 0.87 | | miR-l99a<br>miR-542-3p | 0.9661 | 0.88 | 0.97 |
| Nisenblat | 2019 | Australia | Australians | 51/27 | Plasma | 23.39/31.23 | I II II IV | Non-EMS | U6 | qRT–PCR | NA | Cohort | miR-141* | 1 | 0.8 | 0.92 |
| | | | | | | | | | | | | | miR-145" | 0.86 | 0.55 | 0.86 |
| | | | | | | | | | | | | | miR-923 | 0.85 | 0.55 | 0.77 |
| | | | | | | | | | | | | | miR-145’ | 0.92 | 0.95 | 0.96 |
| | | | | | | | | | | | | | miR-923 | | | |
| | | | | | | | | | | | | | miR-145* | 0.92 | 0.95 | 0.96 |
| | | | | | | | | | | | | | miR-923 | | | |
| | | | | | | | | | | | | | miR-141’ | | | |
| Nisenblat | 2019 | Australia | Australians | 80/39 | Plasma | 29.22/31.36 | 1 II III IV | Non-EMS | U6 | qRT–PCR | NA | Cohort | miR-155 | 0.67 | 0.7 | 0.67 |
| | | | | | | | | | | | | | miR-574-3p | 0.73 | 0.53 | 0.63 |
| | | | | | | | | | | | | | miR-139-3p | 0.7 | 0.57 | 0.62 |
| | | | | | | | | | | | | | miR-155 | 0.83 | 0.51 | 0.71 |
| | | | | | | | | | | | | | miR-574-3p | | | |
| | | | | | | | | | | | | | miR-139-3p | | | |

**Table 1** (continued)

| First author | Year | Country | Race | Cases/controls | Sample type | Mean age case/controls | Stage of Endometnolsis in cases | Trait control | Normalize | Test method | Cut-off | Study design | Markers studied | Sensitivity | Specificity | AUC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rekker | 2015 | Estonia | European | 32/24 | Plasma | 33/31 | I II III IV | Non-EMS | NA | qRT–PCR | NA | Cohort | miR-200a | 0.906 | 0.625 | 0.75 |
| | | | | | | | | | | | | | miR-200b | 0.906 | 0.458 | 0.67 |
| | | | | | | | | | | | | | miR-141 | 0.719 | 0.708 | 0.71 |
| | | | | | | | | | | | | | miR-200a | 0.844 | 0.667 | 0.76 |
| | | | | | | | | | | | | | miR-200b | | | |
| | | | | | | | | | | | | | miR-141 | | | |
| Cho | 2015 | USA and Korea | Mixed | 24/24 | Serum | 33.08/32.1 6 | III IV | Non-EMS | U6 | qRT–PCR | 0.823 | Case-control | let-7d | 0.833 | 1 | 0.91 |
| Wang | 2016 | China | Asian | 59/51 | Serum | 32.34/29.5 6 | I II III IV | Non-EMS | NA | qRT–PCR | 170.20.35 | Cohort | ENST00000482343 | 0.7241 | 0.7174 | 0.72 |
| | | | | | | | | | | | | | ENST0O000544649 NRJ)38395 NR_038452 | 0.7241 | 0.7317 | 0.88 |
| Yuan | 2019 | China | Asian | 90/70 | Serum | 40.54/41.24 | I II III IV | Non-EMS | U6 | qRT–PCR | 3.18 | Case-control | miR-122-5p | 0.947 | 0.905 | 0.91 |
| | | | | | | | | | | | 2.17 | | miR-199a-5p | 0.921 | 0.886 | 0.9 |
| Cosar | 2016 | USA and Korea | Mixed | 24/24 | Serum | 33.08/32.1 6 | III IV | Non-EMS | U6 | qRT–PCR | 0.0688 | Case-control | miR-125b-5p | 1 | 0.96 | 0.97 |
| | | | | | | | | | | | NA | | miR-125b-5p miR-3613-5p miR-451a | 1 | 1 | 1 |
| Maged | 2017 | Egypt | African | 45/35 | Serum | 29.64/29.46 | I II III IV | Non-EMS | U6 | qRT–PCR | 3.24 | case-control | miR-122 | 0.956 | 0.914 | 0.96 |
| | | | | | | | | | | | 2.3 | | mi R-199a | 1 | 1 | 1 |
| Patelsky | 2018 | Austria | European | 36/28 | Plasma | 33.3/37.6 | III–IV | Non-EMS | Six | qRT–PCR | NA | Case-control | miR-154-5p | 0.67 | 0.68 | 0.72 |

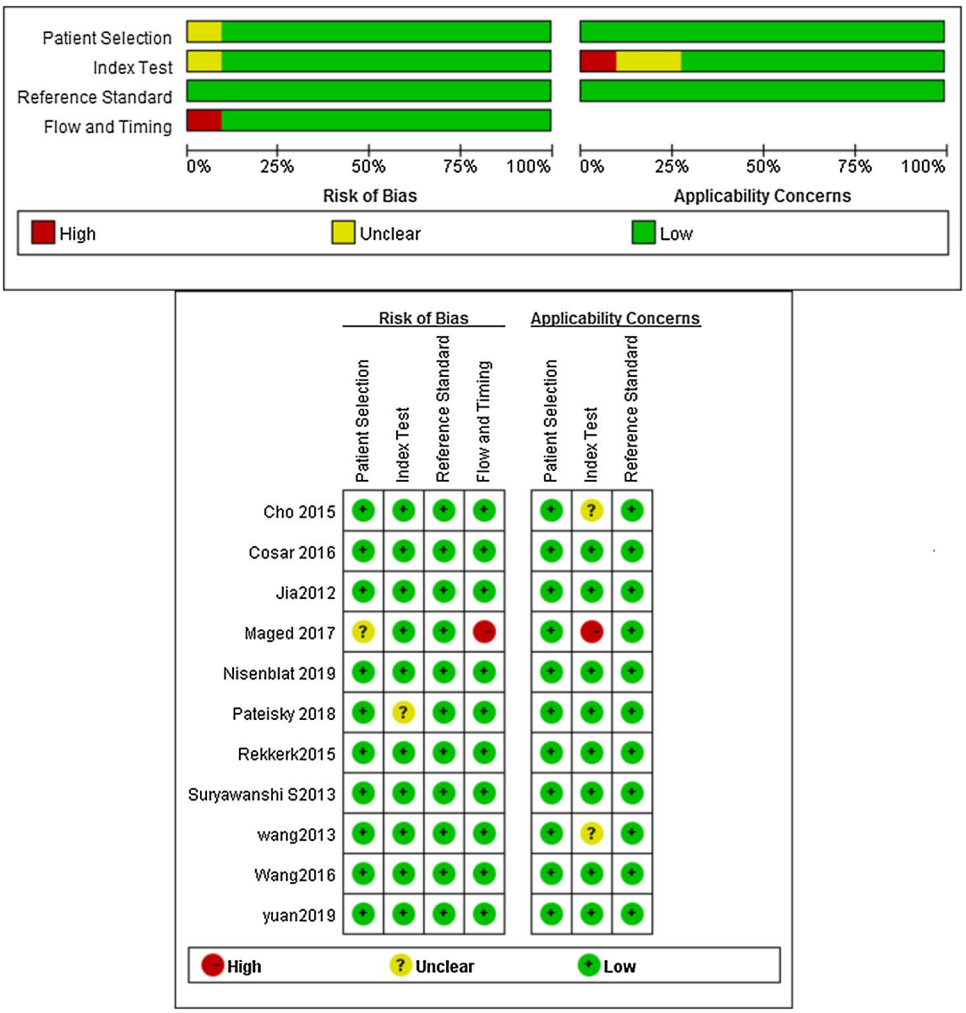



**Fig. 2** QUADAS-2 score results of included studies

## Research characteristics and quality assessment

Basic information from 11 articles is shown in Table 1, extracted and included as follows: (1) the first author; (2) published year: 2013–2019; (3) country: one from Egypt, two from the United States, one from South Korea, one from Australia, one from Estonia, the rest from China; (4) race: six studies were Asian, five studies were European/African/Oceanian; (5) endometriosis type: I, II, III, IV: eight studies, III, IV: three studies; (6) sample type: serum: six studies, plasma: five studies; (7) test method: qRT-PCR. (8) Standard parameters: U6: seven studies, and other parameters: four studies. We evaluated all included studies by the QUADAS-2. The results are summarized in Fig. 4. On the whole, the overall quality of the studies included was relatively high.

According to QUADAS-2 criteria, the quality of eligible studies was assessed by the evaluator independently, as shown in Fig. 2. In general, most studies were considered to be low risk for bias, they included ambiguous risks, index testing, reference criteria etc. There are low potential risk of bias such as patient selection, control population and the applicability of the most of research.

## Diagnostic accuracy of circulating miRNA in endometriosis

The general sensitivity and specificity of the overall study were 0.81 (95% CI 0.76–0.85) and 0.77 (95% CI 0.71–0.82) (Fig. 3). The general PLR and NLR were 3.53 (95% CI 2.66–4.69) and 0.24 (95% CI 0.18–0.33) (Fig. 3). DOR was 14.49 (95% CI 8.32–25.23) (Fig. 4). Area under SROC curve was 0.86 (95% CI 0.83–0.89) (Fig. 5). Taking sensitivity and specificity into account, the $I^2$ was 89.62% (95% CI 87.41%–91.83%) and 81.72% (95% CI 77.15%–86.30%) (Fig. 3). Fagan's likelihood ratio square was used to

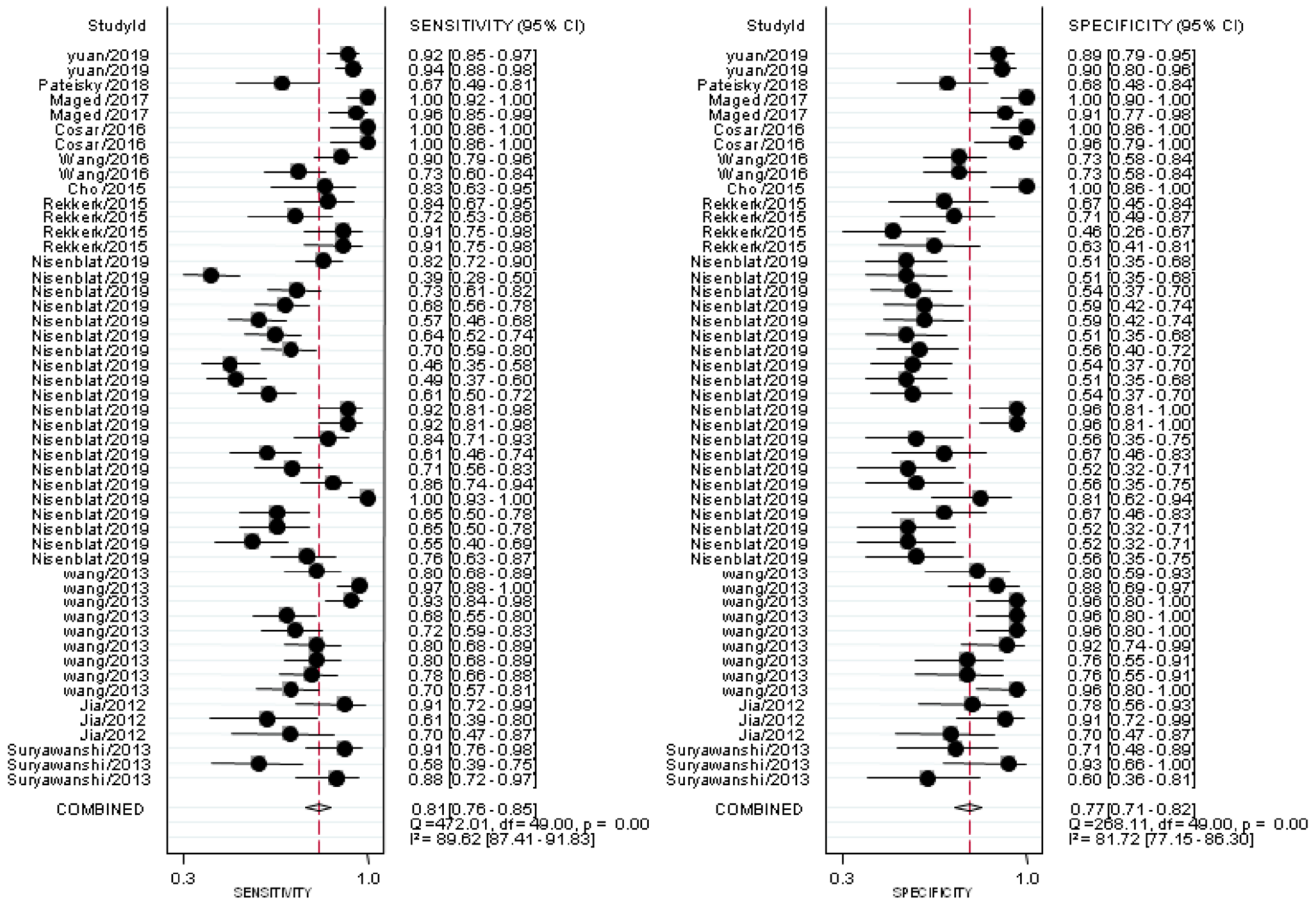



**Fig. 3** Summary of sensitivity and specificity of forest plots for the whole study

determine the probability before and after different predictions. When circulating non-coding RNA assays were performed on all individuals with a 50% pretest probability of endometriosis, the probability of a positive post-test finding endometriosis increased to 78%, while the probability of a negative result decreased to 20%. The HSROC curve was constructed. The estimated values for the sensitivity and specificity of the stratified profile operating points was 0.81 (95% CI 0.76–0.85) and 0.77 (95% CI 0.71–0.82) (Fig. 6). Therefore, circulating non-coding RNA can be used as a non-invasive biomarkers to improve existing diagnostic methods (Fig. 7, supplement Fig.1). The estimated value of "ß" was 0.003 (95% CI − 0.324 to 0.33), the value of "*z*" was 0.02, and the value of "*P*" was 0.986, the value of "λ" was 2.67, which meant that the SROC curve was symmetric. All these results suggested that circulating non-coding RNAs had high accuracy in distinguishing patients with endometriosis from those people without endometriosis (Fig. 7).

## Regression analysis and sensitivity testing

To find potential sources of heterogeneity, we conducted variable analysis of regression. There are many factors that affect the sensitivity, including number of cases (30 or 30) and control group (30 or 30), sample type (serum or plasma), race, evaluation references (U6, others), confirmation results (accurate and general), diagnostic method description (detailed, rough) and several variables. Since most variables might have a relatively large impact on the sensitivity, we performed subgroup analysis based on these factors (Fig. 8). Sensitivity test results were as followed (Fig. 9a–d). The goodness of fit and bivariate normality analysis showed that the bivariate model was moderately robust. Eight outliers were identified by impact analysis. Three outliers were found through outlier detection (Fig. 10).

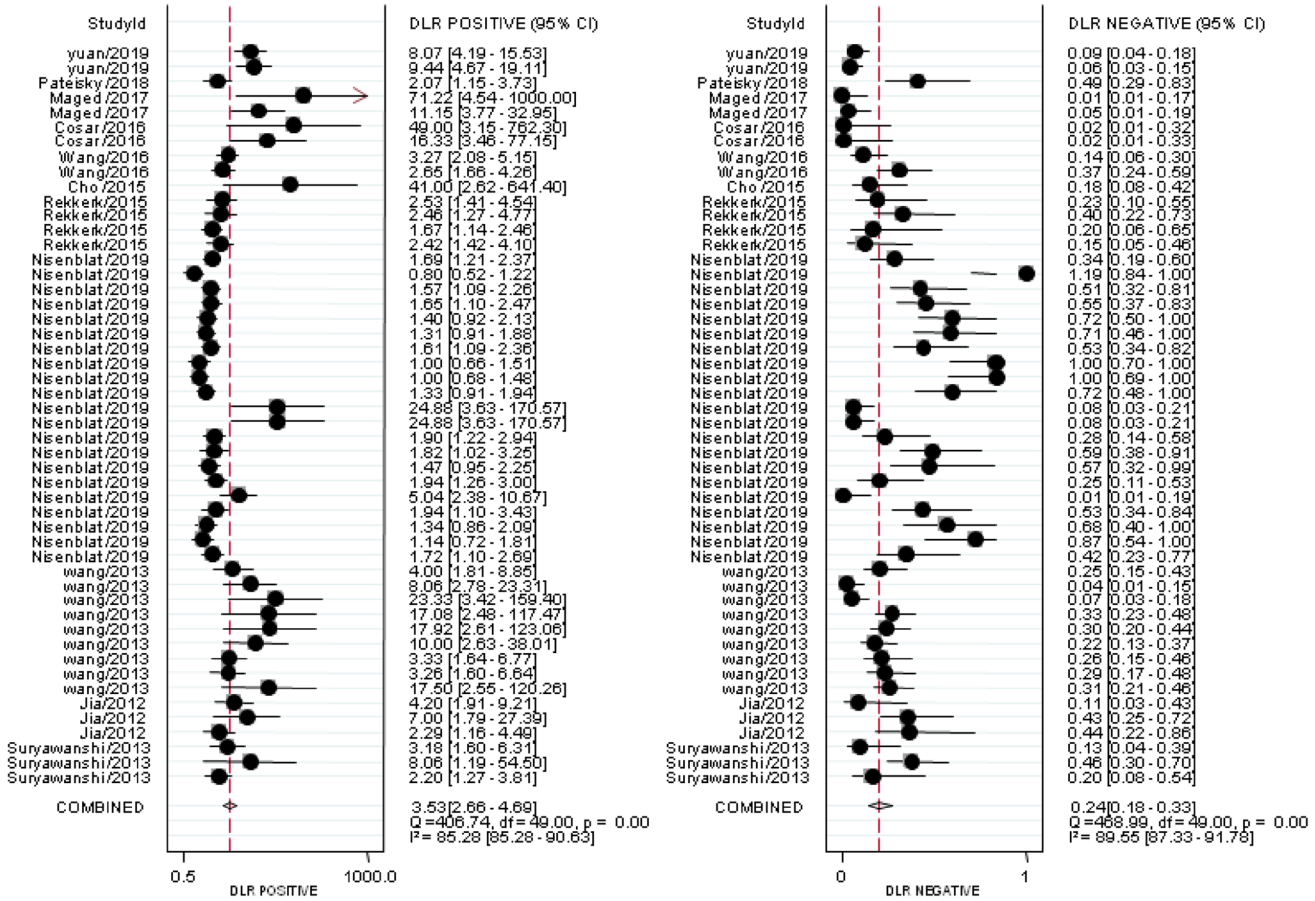



**Fig.4** PLR and NLR forest map of the overall study

## Threshold effects and heterogeneity

ROC planes were used to evaluate threshold effects by reason of differences between cutoff values. We generated the ROC plane by Stata 15.0 and it did not display the atypical shoulder arm appearance, which indicated no threshold effect. The heterogeneity of sensitivity and specificity was 0.8962 (95% CI 0.8741–0.9183) and 0.8172 (95% CI 0.7715–0.8630). It showed obvious heterogeneity. Thus, a meta-regression analysis was performed to explore potential sources of sensitivity and specificity heterogeneity.

## Publication bias

Deeks' funnel plot symmetry test (Fig. 11) searched for potential publication bias. In this study, the *P* value of linear regression was 0.19, which indicated no publication bias [34].

## Discussion

The rapid development of a new generation of sequencing technology had identified a large number of genes in the process of expression disorders [35–37]. In recent years, circulating non-coding RNAs had been identified as a regulator of gene expression and played an important role in the occurrence and development of endometriosis [38–41]. Since circulating non-coding RNA can be easily collected from body fluids (such as plasma, serum, urine and secretions) in a non-invasive manner, therefore, more and more evidence implied that humoral-based circulating non-coding RNAs could be the potential new non-invasive biomarkers for the detection and diagnosis of endometriosis [23, 25–29, 31, 42–51]. Although three previous meta-analyses of the diagnostic significance of circulating non-coding RNA in endometriosis were published a few years ago, two of these studies included more non-invasive markers that evaluated

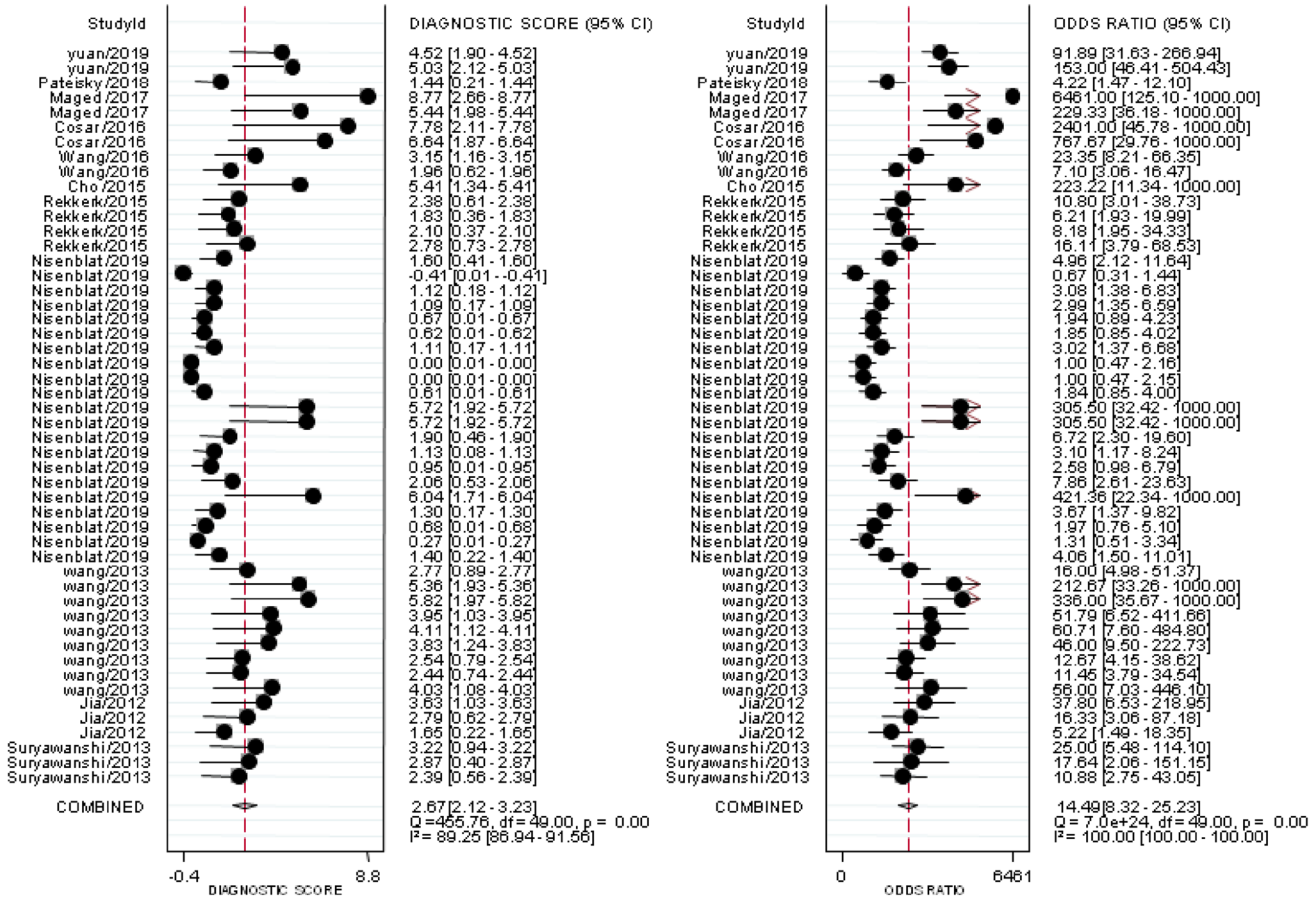



**Fig. 5** The overall diagnostic ratio summarized in the study DOR forest diagram

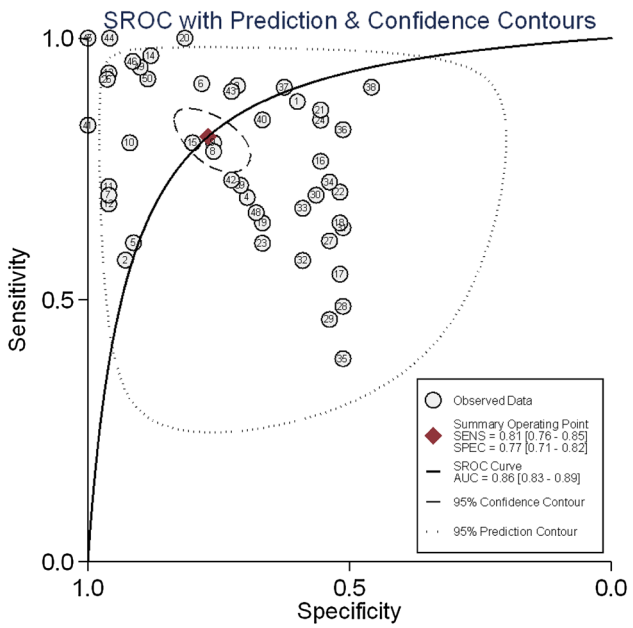



**Fig. 6** SROC curve

the scientific and practical diagnosis of endometriosis and paid little attention to circulating non-coding RNAs. Another paper analyzed the expression level of circulating non-coding RNAs in various studies of endometriosis and its possible diagnostic potential, and in spite of this, it failed to provide comprehensive diagnostic data (overall sensitivity, specificity and AUC etc.). To avoid the limitations of the previous meta-analysis, we performed this meta-analysis. We accurately identified the overall clinical potential of circulating non-coding RNAs in the detection and diagnosis of endometriosis in a non-invasive manner. The pooled overall sensitivity and specificity of this study were 0.81 (95% CI 0.76–0.85) and 0.77 (95% CI 0.71–0.82) (Fig. 3) [45]. The $I^2$ for sensitivity and specificity was 89.62% (95% CI 87.41%–91.83%) and 81.72% (95% CI 77.15%–86.30%), which indicated significant heterogeneity between these studies. Thus, meta-regression analysis explored potential sources of sensitivity and specificity heterogeneity. The race, standard parameters, sample type, number of cases and controls of the results had a significant impact on inter-study heterogeneity (Fig. 8). The pooled PLR and NLR were 3.53 (95% CI 2.66–4.69) and 0.24 (95% CI 0.18–0.33) (Fig. 3).

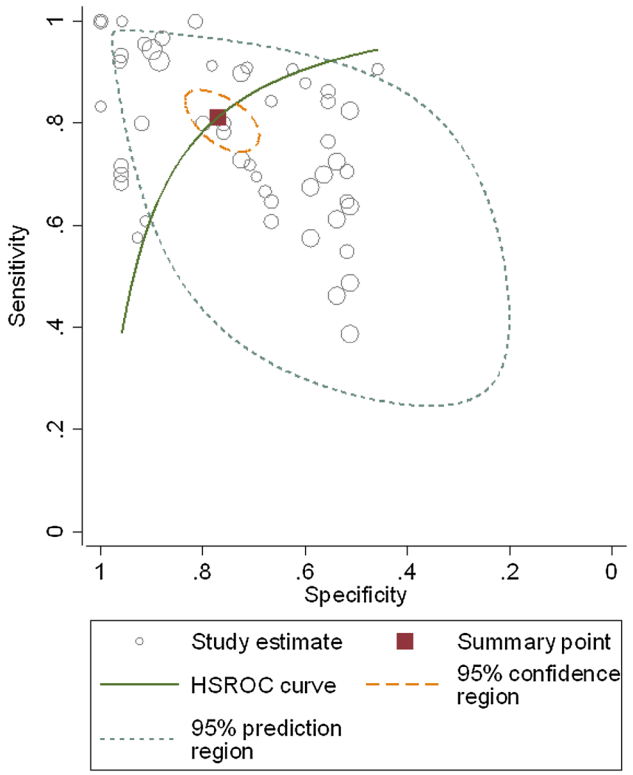



**Fig. 7** The HSROC curve

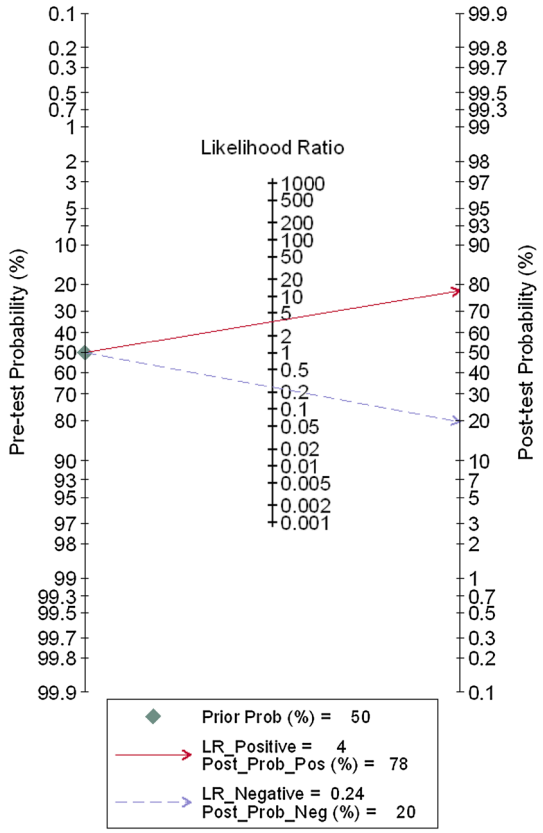
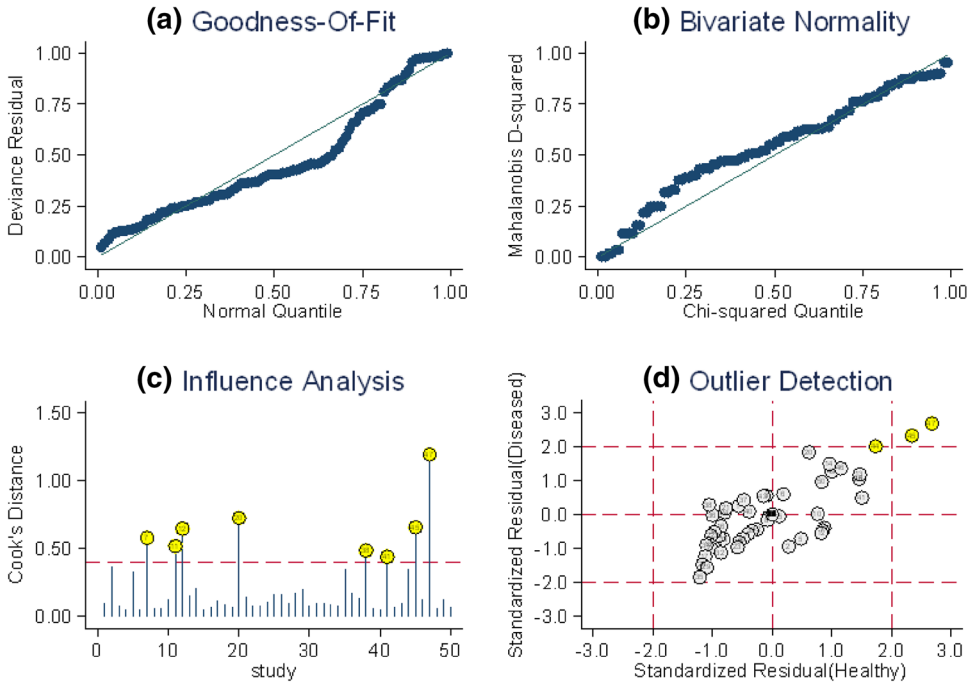



**Fig. 8** Fagan's likelihood ratio square

**Fig. 9** Impact analysis and outlier detection (note: (**a**) goodness of fit (**b**) bivariate normality (**c**) impact analysis, and (**d**) outlier detection.)



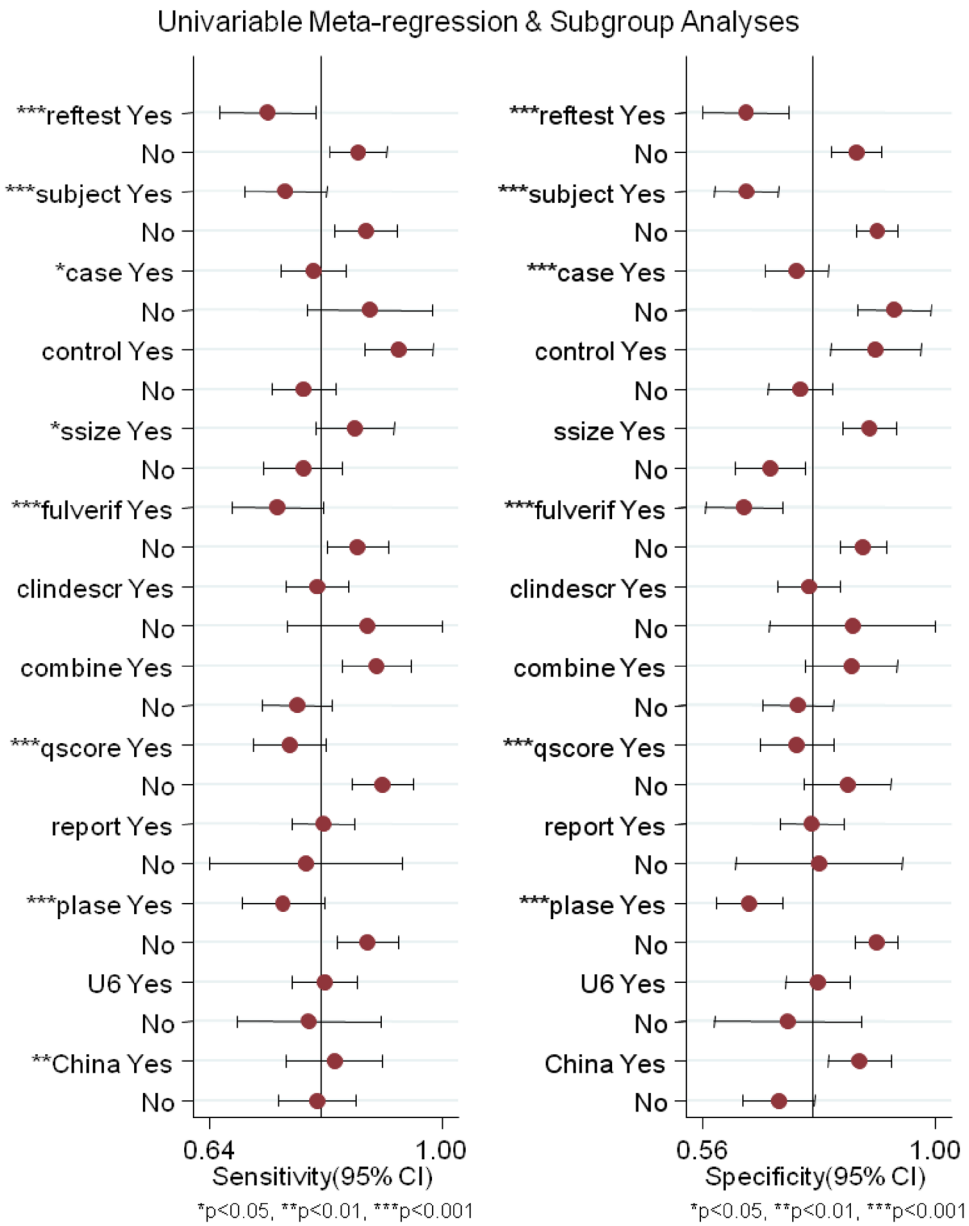



**Fig. 10** Regression analysis and subgroup analysis (note: asterisked factors are potential factors for heterogeneity)

DOR was 14.49 (95% CI: 8.32–25.23) (Fig. 4 [50, 52]. The area under the SROC curve was 0.86 (95%CI 0.83–0.89), and the estimated value of stratified profile operating points for sensitivity and specificity were 0.81 (95% CI 0.76–0.85) and 0.77 (95% CI 0.71–0.82). The estimated value of "$\beta$" is 0.003 (95% CI −0.324 to 0.33), the value of "$z$" is 0.02, and the value of $P$ is 0.986, which meant that the SROC curve is symmetric. The value of Lambda is 2.67 (95% CI 2.12–3.23). Fagan's nomogram determined the post-test probabilities generated by different predictive test probabilities to explore the clinical value of cyclic non-coding RNA. (Fig. 7). All these results indicated that circulating non-coding RNAs has relatively high accuracy in the diagnosis of endometriosis compared to others.

For comprehensive evaluation, some limitations of this study should still be emphasized. First, although most eligible studies mentioned the stage of endometriosis, early-stage diagnosis was not made by circulating non-coding RNAs. Most non-coding RNAs remain to be identified. There may be other classes of undiscovered RNAs, and most of their functions are unknown [51]. Non-coding RNAs are involved in numerous physiological and pathological processes. Therefore, non-coding RNAs as diagnostic markers need to be combined with clinical history, physical examination and other auxiliary examinations to comprehensively determine whether patients have this disease. Each included study has its own cutoff value of demarcation standard, which cannot achieve effective unification. The change in cutoff value

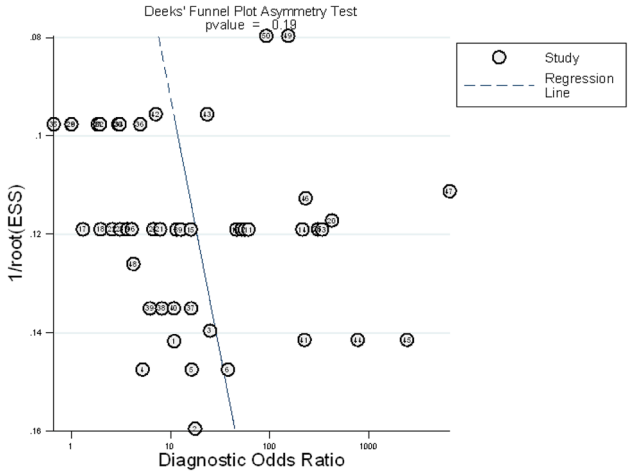



**Fig. 11** Deeks' funnel plot symmetry test was used to assess publication bias

always results in sensitivity and specificity influencing each other. Therefore, the validity of non-coding RNAs as biological diagnostic markers in a group of patients needs to be verified again to establish a reasonable threshold standard. Therefore, this study was not able to evaluate the difference in the accuracy of early diagnosis of circulating non-coding RNAs in patients with endometriosis at different stages. Second, not all studies reported truncation values of circulating non-coding RNAs, which largely led to potential sources of heterogeneity. Third, the sample type was inconsistent, including serum and plasma. Due to the limited size of each study, a subgroup analysis of sample types could be explored. Fourth, the studies included were not blind comparative test studies, which means that there might be subjective judgments that may result in poor quality in QUADAS-2. Despite these limitations, our study is the most comprehensive meta-analysis to assess the diagnostic value of circulating non-coding RNAs in patients with endometriosis.

## Conclusion

In summary, the results of this meta-analysis imply that circulating non-coding RNAs are relatively accurate in distinguishing patients of endometriosis and provide comprehensive precise evidence for circulating non-coding RNAs as potential non-invasive biomarkers in detection and diagnosis. However, they are not the only diagnostic markers. We need to comprehensively analyze the clinical information and condition of patients. Furthermore, there is an urgent need for well-designed prospective randomized controlled and blind studies with large sample sizes in different populations to further confirm the scientificity and applicability of our findings.

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## Compliance with ethical standards

**Conflict of interest** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval** The authors declare that there are no ethical issues, because this meta-analysis required the study of previous studies without any intervention of the patients.

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