Original Article

Diagnosis accuracy of the miR-200 family tumor marker series in ovarian cancer: a systematic review and meta-analysis

Li Liu[1#], Pan Li[2#], Qin Wang[3], Chunting Dong[4], Meijun Guo[5], Rui Wang[2]

[1]Department of Pathology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China; [2]Department of Nuclear Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China; [3]Delivery Room, Chengdu Women's and Children's Central Hospital, Chengdu, China; [4]Clinical Laboratory, The Fifth Hospital of Sichuan Province, Chengdu, China; [5]Clinical Laboratory, Chengdu Children Special Hospital, Chengdu, China

Contributions: (I) Conception and design: L Liu; (II) Administrative support: R Wang; (III) Provision of study materials or patients: P Li; (IV) Collection and assembly of data: Q Wang; (V) Data analysis and interpretation: C Dong, M Guo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Rui Wang. Department of Nuclear Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610072, China. Email: wangrui100423@163.com.

Background: To evaluate the diagnosis value of the microRNA-200 family in ovarian cancer patients. However, there is much controversy regarding the diagnosis of miR-200. Therefore, it is necessary to use meta method to further confirm the significance of diagnosis role of the miR-200 family tumor marker series in ovarian cancer.

Methods: We performed a careful literature search of the PubMed, EMBASE, and Web of Science databases and search language is English for articles related to ovarian cancer diagnose and the miR-200 family. The retrieval period was from the date of establishment of the database until September 20, 2021. The search keywords included microR-200, microR-200a, microR-200b, microR-200c, ovarian cancer, ovarian carcinoma, ovarian tumor, and sensitivity (SEN), specificity (SPE), area under the curve (AUC) were then calculated to estimate the diagnostic accuracy of the miR-200 family, and meta-analysis was performed using Stata 15.0 software.

Results: Five articles were included in the meta-analysis. The diagnostic value of miR-200a in epithelial ovarian cancer (EOC) was expressed as 0.76 (95% CI: 0.67–0.84) by SEN; the combined SPE was 0.71 (95% CI: 0.49–0.86); the pooled AUC was 0.79 (95% CI: 0.76–0.83). The diagnostic value of miR-200b in EOC was expressed by SEN of 0.84 (95% CI: 0.76–0.90) and SPE of 0.73 (95% CI: 0.48–0.88). Combined AUC was 0.86 (95% CI: 0.83–0.89). The diagnostic value of miR-200c in EOC was 0.90 (95% CI:0.69–0.97), and the SPE was 0.87 (95% CI: 0.37–0.99). Combined AUC was 0.94 (95% CI: 0.92–0.96).

Discussion: The miR-200 family may be a marker for the diagnosis evaluation of ovarian cancer patients.

Keywords: miR-200 family; gynecological tumors; diagnose of survival; survival time; systematic review

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Introduction

Domestic epidemiological investigations have shown that ovarian cancer accounted for 2.51–3.76% of the incidence and 1.98–3.05% of the malignant tumor-related deaths in females over the same period (1). Some known biomarkers are controversial, including tiny RNA (microRNA, miRNA), which has become a research hotspot over the past decade. miRNAs have a significant effect on the occurrence

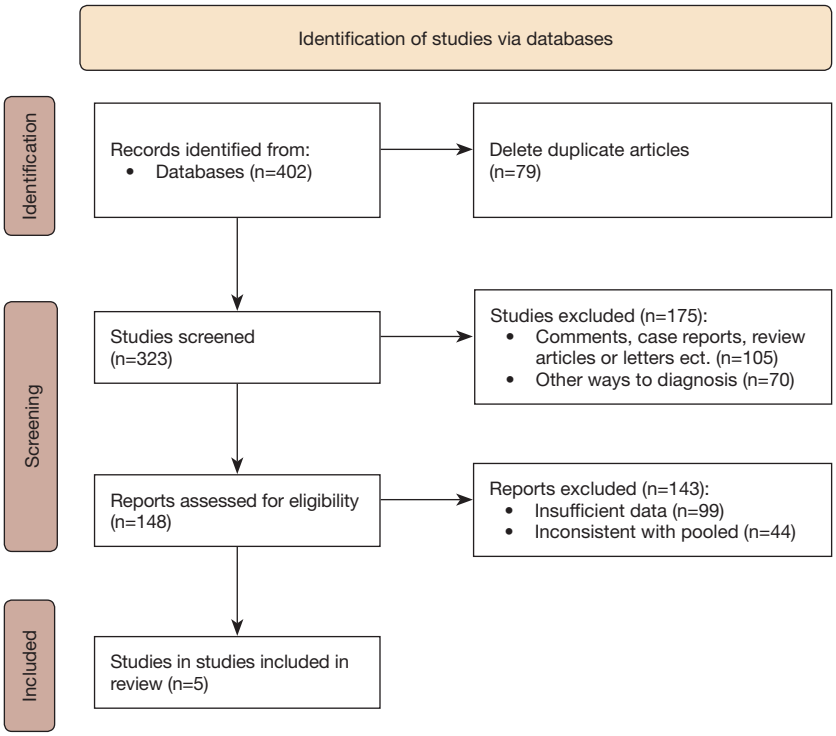

Figure 1 Literature screening flow chart.

and development of ovarian cancer, the most studied and controversial of which is microR-200, which is a group of tumor suppression-related miRNA families that is currently known to have five miRNA compositions. While the miR-200 family varies Different results of miRNA assessed clinical diagnosis value in ovarian cancer patients.

miRNA is a class of non-coding RNA consisting of 17 to 25 nucleotides, which is widely involved in human physiological and pathologic metabolic processes, and regulates the expression levels of target genes in a post-transcriptional regulatory manner (2).

However, Since the sensitivity (SEN) and specificity (SPE) of the miR-200 family for the diagnosis of ovarian cancer are significantly different in different clinical studies, it is essential to determine the accuracy of the diagnosis of ovarian cancer. (3-5). Many people have different opinions about the accuracy of miR-200 in ovarian cancer, and there is no consensus (6-8). Therefore, it is necessary to use meta method to further confirm the significance of this combined detection method in the diagnosis of ovarian cancer. We present the following article in accordance with the PRISMA-DTA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-864/rc).

Methods

Retrieval strategy

We performed a careful literature search of the PubMed, EMBASE, and Web of Science databases and search language is English. The search keywords included microR-200, microR-200a, microR-200b, microR-200c, ovarian cancer, ovarian carcinoma, ovarian tumor, etc. The retrieval period was from the date of establishment of the database. At the same time, the included references were traced and relevant conference papers were manually searched to retrieve related information. Two reviewers independently evaluated the included literature (*Figure 1*).

Literature inclusion criteria

(I) Studies that limited the research scope to the diagnose of patients with ovarian cancer; (II) articles published in English; (III) the group was measured Expression of miRNA in tissue or serum; (IV) the cut-off value, SEN and

Table 1 Basic clinical features of the 5 included studies

First author	Year	Country	miRNA	Cancer type	Tumor/control	Stage
Meng (9)	2016	Germany	200a, 200b, 200c	EOC	163/52	I–IV
Zuberi (10)	2015	India	200a, 200b, 200c	EOC	19/51	IV
Zhang (11)	2022	China	200a, 200b	EOC	55/30	III–IV
Hannan (12)	2021	Australia	200c	EOC	14/15	III–IV
Kan (13)	2012	Australia	200a, 200b, 200c	EOC	28/28	III

EOC, epithelial ovarian cancer.

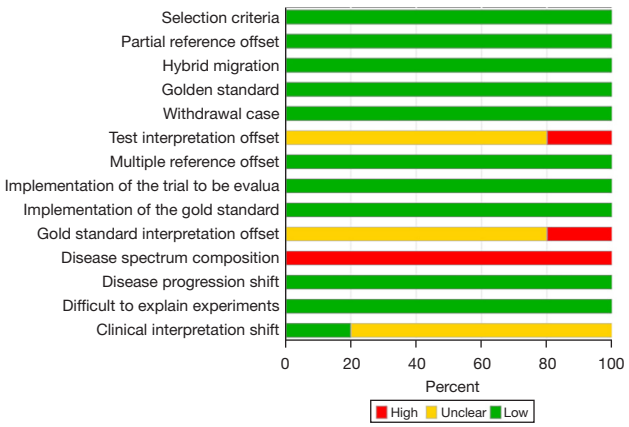

Figure 2 Literature quality evaluation chart. Risk of bias graph.

SPE for diagnostic value.

Literature exclusion criteria

(I) Experimental study, and research; (II) studies that investigated the expression of a group of miRNAs, but the miR-200 family was not studied alone; (III) articles that did not include diagnosis data 95% CI, and other related information. Disagreements between the two reviewers were resolved by a third reviewer. Considering that there is no broad consensus on meta-analysis literature quality scores for diagnosis studies, and the necessity and credibility of scoring are controversial, we did not evaluate the obtained literature component.

Data extraction

Two reviewers independently extracted the data included in the literature, which included the following: We extracted the following data for the diagnostic value of the miR-200 family: first author name, publication year, country, miR-200 family members, cancer type, number of epithelial ovarian cancer (EOC) patients and control group, ovarian pain stage, miR-200, SEN and SPE of the family.

Quality assessment

Quality assessment based on QUADAS guidelines was performed for the 7 included studies. The highest score possible is 14.

Statistical analysis

STATA software version 15.0 is used for data analysis. The SEN and SPE were analyzed. The overall diagnostic accuracy was evaluated by the summary receiver operator characteristic (SROC), and the area under SROC curve (AUC) was calculated. The heterogeneity across studies were assessed by Q test and I^2 statistics calculation. If P-value is less than 0.05 for Q test or I^2 value is greater than 50%, heterogeneity is substantial, and the random effects model will be adopted.

Result

Literature retrieval results and characteristics of the included studies

A total of 402 relevant documents were initially retrieved. 79 duplicated articles were deleted, and a further 175 were deleted after screening titles and abstracts.

After the final review of the full text except 143. Finally, a total of 5 eligible articles remained (9-13).

Basic features of the included studies

The basic features of the included studies are shown in *Table 1*.

Quality evaluation of the included studies

The 5 included studies (9-13), were of relatively good overall quality (based on QUADAS-2 criteria) in *Figure 2*.

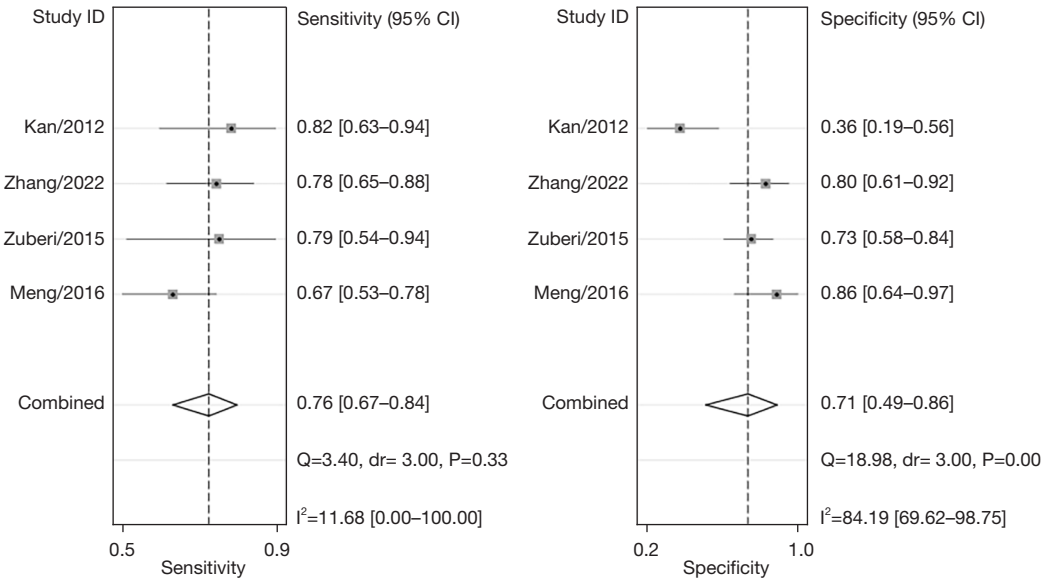

Figure 3 Sensitivity and specificity plotted graph for the diagnostic of miR-200a in epithelial ovarian cancer.

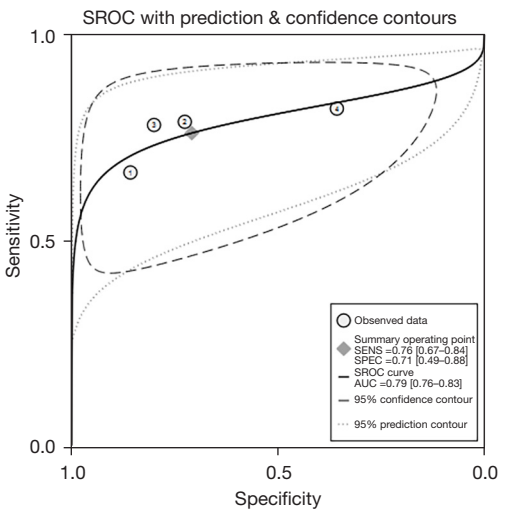

Figure 4 SROC curve plotted graph for the diagnostic value of miR-200a in epithelial ovarian cancer. SROC, summary receiver operator characteristic; AUC, area under SROC curve.

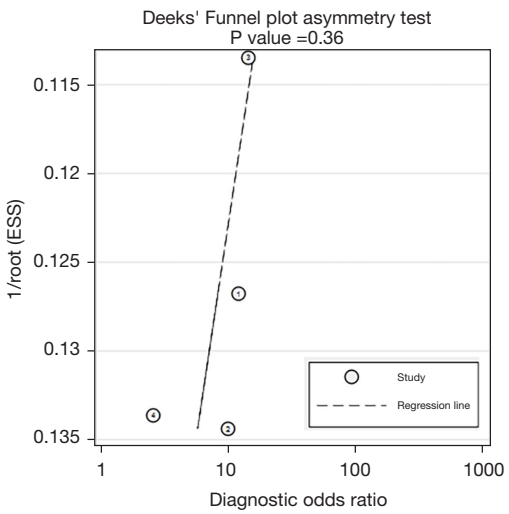

Figure 5 Funnel plot of publication bias of miR-200a in epithelial ovarian cancer. ESS, effect sizes.

Total analysis of the diagnostic value of miR-200a for EOC

The diagnostic value of Mir-200a in EOC was investigated from Five studies, and four of the articles describe miR-200a.The detection methods used in this study were RT-QPCR, NEst-PCR and NGS. The results were as follows: the pooled SEN was 0.76 (95% CI: 0.67–0.84); The combined SPE was 0.71 (95% CI: 0.49–0.86): these results are illustrated by the forest map in *Figure 3*. The diagnostic performance of miR-200 family was determined by SROC curve analysis, miR-200a showed excellent diagnostic accuracy, with a combined AUC of 0.79 (95% CI: 0.76–0.83) in *Figure 4*. Results No significant heterogeneity was found. These results suggest that Mir-200a has excellent diagnostic performance for EOC. The Deeks' Funnel plot shows that there is no publication bias, and *Figure 5* shows that there is no publication bias in diagnostic studies.

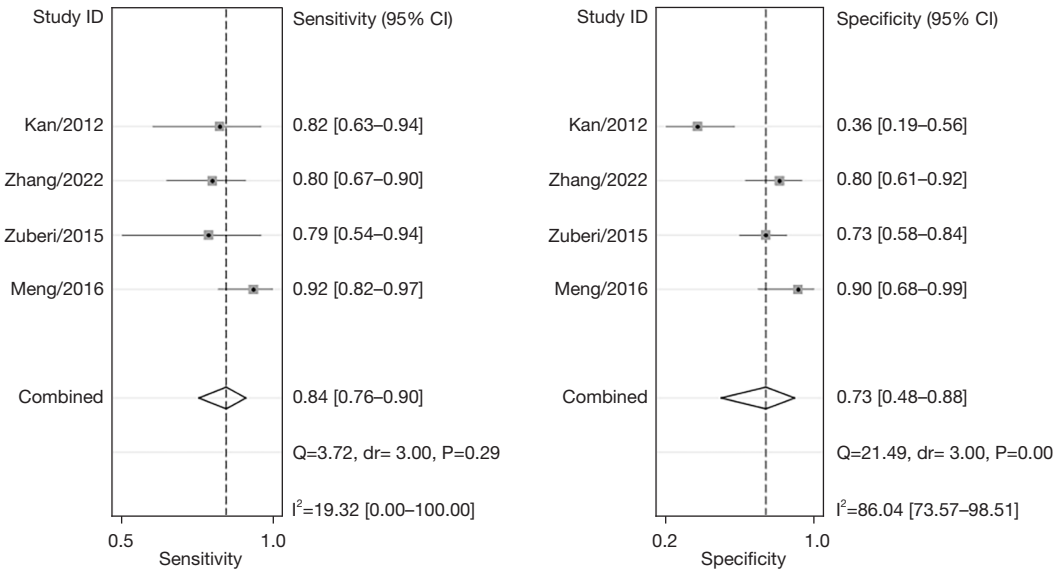

Figure 6 Sensitivity and specificity plotted graph for the diagnostic of miR-200b in epithelial ovarian cancer.

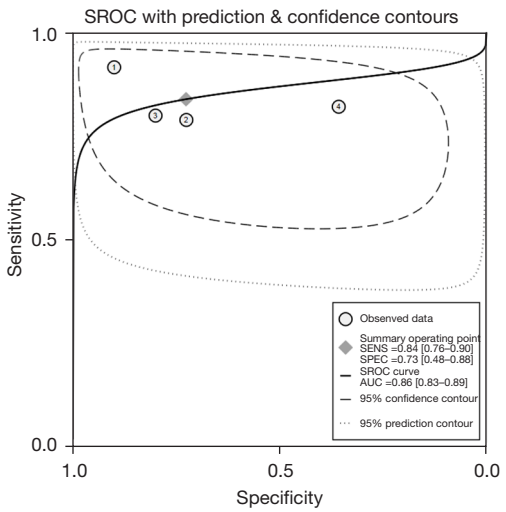

Figure 7 The SROC curve plotted graph for the diagnostic value of miR-200b in epithelial ovarian cancer. SROC, summary receiver operator characteristic; AUC, area under SROC curve.

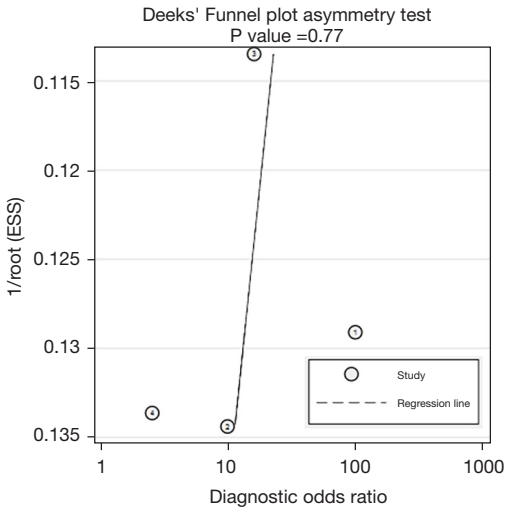

Figure 8 Funnel plot of publication bias of miR-200b in epithelial ovarian cancer. ESS, effect sizes.

Total analysis of the diagnostic value of miR-200b for EOC

In this study, the diagnostic value of miR-200b in EOC was demonstrated, and four of the articles describe miR-200b. A total of 578 subjects were involved in this meta-analysis. The results were as follows: pooled SEN was 0.84 (95% CI: 0.76–0.90) and combined SPE was 0.73 (95% CI: 0.48–0.88); These results are illustrated by a forest map in *Figure 6*. The diagnostic performance of miR-200b was determined by SROC curve analysis. *Figure* 7 miR-200b showed excellent diagnostic accuracy, with a summary AUC of 0.86 (95% CI: 0.83–0.89), and the diagnostic accuracy of miR-200b for EOC was as high as 86%, so it can be known that the accuracy of miR-200b is very close to the gold standard. Results No significant heterogeneity was found. These results suggest that Mir-200b has excellent diagnostic performance for EOC. Deek's diagram shows P>0.05, and there is no publication bias. *Figure 8* shows that there is no

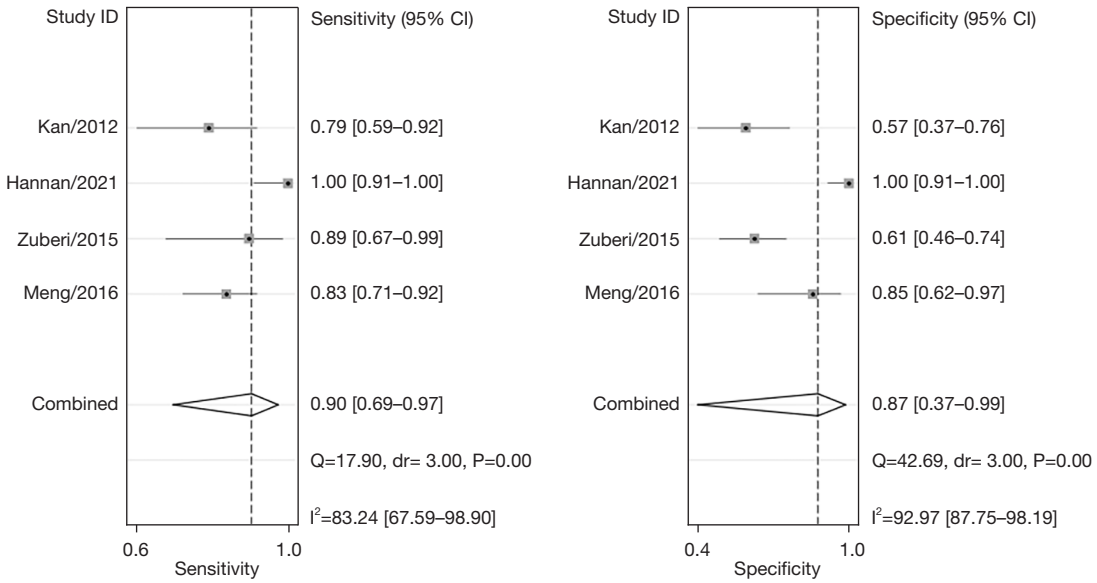

Figure 9 Sensitivity and specificity plotted graph for the diagnostic of miR-200c in epithelial ovarian cancer.

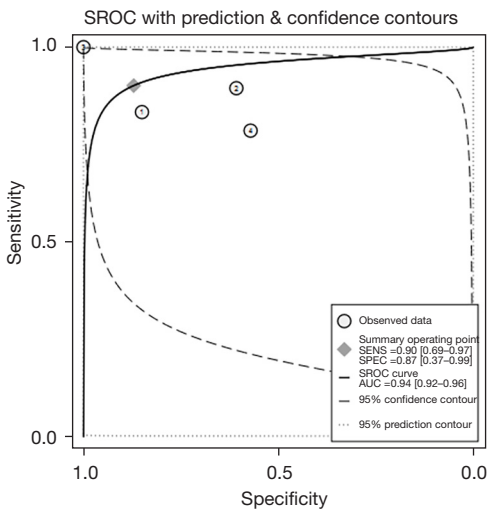

Figure 10 The SROC curve plotted graph for the diagnostic value of miR-200c in epithelial ovarian cancer. SROC, summary receiver operator characteristic; AUC, area under SROC curve.

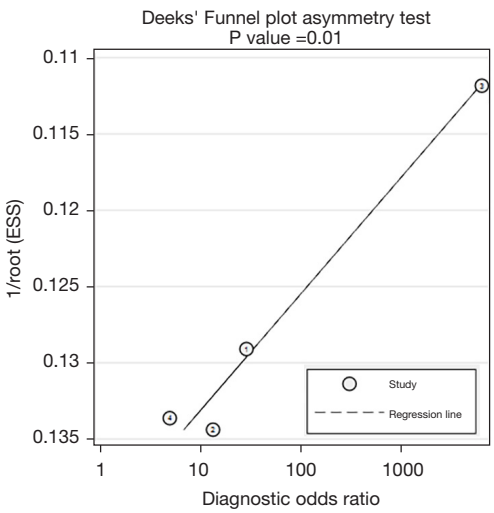

Figure 11 Funnel plot of publication bias of miR-200c in epithelial ovarian cancer. ESS, effect sizes.

publication bias in diagnostic studies.

Total analysis of the diagnostic value of miR-200c for EOC

The diagnostic value of Mir-200c in EOC was investigated from five studies, and four of the articles describe miR-200c. The results were as follows: the pooled SEN was 0.90 (95% CI: 0.69–0.97); The combined SPE was 0.87 (95% CI: 0.37–0.99): these results are illustrated by the forest map in *Figure 9*. The diagnostic performance of miR-200c was determined by SROC curve analysis, miR-200c showed excellent diagnostic accuracy, with a combined AUC of 0.94 (95% CI: 0.92–0.96) in *Figure 10*. Results No significant heterogeneity was found. These results suggest that miR-200c has excellent diagnostic performance for EOC. The Deeks' Funnel plot shows P<0.05 in *Figure 11*.

Discussion

Five articles were included in the meta-analysis. The diagnostic value of miR-200a in EOC was expressed as 0.76 (95% CI: 0.67–0.84) by SEN; The combined SPE was 0.71 (95% CI: 0.49–0.86); the pooled AUC was 0.79 (95% CI: 0.76–0.83).

The diagnostic value of miR-200b in EOC was expressed by SEN of pooled SEN was 0.84 (95% CI: 0.76–0.90) and combined SPE was 0.73 (95% CI: 0.48–0.88). Combined AUC was 0.86 (95% CI: 0.83–0.89). The diagnostic value of miR-200c in EOC was 0.90 (95% CI: 0.69–0.97), and the SPE was 0.87 (95% CI:0.37–0.99). Combined AUC was 0.94 (95% CI: 0.92–0.96). As result of this, the overall miR-200 family can be used as a highly accurate diagnostic marker in EOC (14). In summary, serum miR-200a, B, and C levels were elevated in women with EOC. Overexpression of miR-200 improves survival and leads to proliferation problems (15-17).

However, our meta-analysis still has some limitations. The included studies were evaluated using different Mir-200. Second, the incidence of EOC varies from country to country. Thirdly, the expression of miR-200 family was examined in different specimen types, blood and tissue sample. Fourthly, miRNA expression may vary according to patients' age, tumor grade, degree of differentiation, tumor size, etc. In conclusion, a large number of clinical studies are needed to confirm this.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-864/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-864/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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