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Diagnostic value and clinical significance of serum miR-134-5p combined with uterine artery color Doppler ultrasound parameters in endometriosis

Shan Jiang[1†], Zhaoning Xu[2†], Xiyan Shao[3*], Jinlan Liang[3], Ming Li[4], Lu Bai[5] and Ting Wang[6*]

Abstract

Objective To exploit the combination diagnostic performance of serum microRNA-134-5p (miR-134-5p) and color Doppler ultrasound in patients with endometriosis patients.

Methods Quantitative real time polymerase chain reaction (qRT-PCR) analysis was applied to measure relative abundance of miR-134-5p in serum of patients with endometriosis and gynecological benign diseases. Calculation of uterine artery blood flow parameters was conducted using Color Doppler ultrasound. Receiver operating characteristic (ROC) curve was established to evaluate the diagnostic capacity of miR-134-5p and Doppler parameters. Kaplan-Meier method was used for the analysis of recurrence-free survival rate.

Results Compared with the control group, serum miR-134-5p expression was remarkably diminished in endometriosis patients ($P<0.001$). End-diastolic velocity (EDV) and peak systolic velocity (PSV) were notably decreased in endometriosis patients compared with the control group ($P<0.001$), while pulsatility index (PI) and resistance index (RI) were distinctly increased ($P<0.001$). Serum miR-134-5p expression was positively correlated with EDV ($r=0.5777$, $P<0.0001$) and PSV ($r=0.6945$, $P<0.0001$), but negatively correlated with PI (r=-0.6382, $P<0.0001$) and RI (r=-0.6247, $P<0.0001$). The area under the ROC curve (AUC) of serum miR-134-5p combined with Doppler parameters was 0.905, with the sensitivity of 87.40%, and the specificity of 82.29%. The recurrence-free survival time was shorter in patients with low miR-134-5p expression than those with high miR-134-5p expression ($P=0.013$).

Conclusion A better diagnostic value of endometriosis detection could be obtained when serum miR-134-5p was combined with Doppler parameters.

Keywords MiR-134-5p, Diagnosis, Doppler ultrasound, Endometriosis

†Shan Jiang and Zhaoning Xu contributed equally to this work.

*Correspondence:
Xiyan Shao
shaoxiyan9523@163.com
Ting Wang
tingwang753@163.com

Full list of author information is available at the end of the article

Introduction

Endometriosis is a common, benign, chronic inflammatory and oestrogen-dependent gynecological disorder of childbearing age, the incidence of which has increased in recent years [1, 2]. The active endometrial cells and glands of patients abnormally grow outside the endometrium and these ectopic endometrial cells display pathological hyperplasia [3]. The common symptoms include chronic pelvic pain, dysmenorrhea, difficulty in sexual intercourse, infertility, depression, anxiety, periodic intestinal disease and fatigue [4, 5]. Conventional imaging examinations, such as ultrasound, have high sensitivity and specificity for endometriosis, but this method is affected by the professional level of operators. At present, laparoscopy is the gold standard, but it relies heavily on the professional knowledge of gynecologists [6]. Although endometriosis is regarded as a benign lesion in histology, it still has the features of invasiveness and distant metastasis [7, 8]. So, it requires appropriate examinations to confirm the detection as soon as possible and to provide reasonable treatments for decreasing its adverse effects. At present, the histologically confirmed diagnostic laparoscopy is the gold standard, but it is invasive and accompanied by associated with potential perioperative and postoperative complications [9, 10]. What's worse, the high rate of post-operative recurrence and the unfavorable prognosis of infertility can have a serious impact on the health and quality of life of the patient [11]. It is of great significance to develop serum biomarkers with high sensitivity and specificity for early diagnosis and active treatment of endometriosis, and to improve the prognosis.

MicroRNAs (miRNAs) are a group of short, single-stranded RNA molecules, with a length of 20–22 nucleotides [12]. Highly conserved in humans, miRNA acts a pivotal role in physiological and pathological behaviors such as apoptosis, stress response, and tumor growth, by modulating mRNA via post-transcriptional regulation [13]. Recent reports have shown that aberrant expression of miRNA is related to a wide range of disorders, such as tumor, inflammatory and gynecological diseases [14]. In a very stable manner, miRNAs can be discovered in almost all human body fluids, such as plasma and serum [15]. Abnormal blood miRNA expression levels may be a reflection of normal physiological processes changes, especially gynecological diseases [16]. It was reported that serum exosomes microRNA-134-5p (miR-134-5p) was screened out via sequencing as a potential diagnostic biomarker for parathyroid carcinoma [17]. However, its diagnostic capacity for endometriosis is seldom reported.

In the current research, we measured the relative abundances of miR-134-5p in serum samples of patients with endometriosis, and analyzed the Doppler parameters of the uterine artery. The diagnostic precision of serum miR-134-5p expression combined with Doppler parameters was evaluated in patients with endometriosis using receiver operating characteristic (ROC) curve.

Method and materials

Ethics statement

This study was supported by the Ethics Committee of The Second Affiliated Hospital, School of Medicine, The Chinese University of Hong Kong. Before the sample collection, all the subjects were fully informed and signed the informed consent form voluntarily (Ethical approval number: 2019−359).

Study design

The research retrospectively enrolled 119 endometriosis patients who were subjected to laparoscopy performed by an experienced team led by the same gynecologist in The Department of Gynecology in The Second Affiliated Hospital, School of Medicine, The Chinese University of Hong Kong, as study group (endometriosis group). All endometriosis patients were confirmed by pathological examination. The diagnostic criteria were based on the *Specifications for the Diagnosis and Treatment of Endometriosis* [*Chinese Journal of Obstetrics and Gynecology*, 2015(3)] issued by the Obstetrics and Gynecology Branch of Chinese Medical Association. In addition, another 96 patients with gynecological benign diseases who were subjected to gynecological and ultrasonography examinations at the same period were selected as the control group in this case-control study.

Baseline characteristics

The basic information was recorded and summarized, including age, body mass index (BMI), smoking, alcohol intake, infertility, nulliparity, dysmenorrhea, dyspareunia, chronic pelvic pain, menstrual disorder, and rASRM (revised American Society for Reproductive Medicine). Endometriosis was divided into mild (stages I+II), moderate to severe (stages III+IV) based on the rASRM staging criteria [18].

Inclusion and exclusion criteria

Inclusion criteria: meeting the diagnostic criteria for endometriosis; no use of hormones and hormone-like drugs within 3 months prior to operation; child bearing age (20–45 years); completion of informed consent.

Exclusion criteria: there are other types of gynecological diseases, such as uterine fibroids and ovarian diseases; the existence of intrauterine fluid accumulation; the presence history of uterine surgery, such as caesarean deliveries and myomectomy, and congenital uterine malformations; in pregnancy, breastfeeding; accompanied by any other major systemic diseases, especially malignant tumor.

Sample collection

The fasting venous blood was obtained in anticoagulation tubes from patients with endometriosis before operation and controls. After centrifugation, the supernatant was obtained and stored at -80℃ for further analysis.

Follow-up analysis

All endometriosis patients were followed up for 3 years by telephone and outpatient service. Pathological examination was used to diagnose recurrence of ovarian endometriosis.

Real-time quantitative PCR (qRT-PCR)

TRIzol reagents were applied to isolate total RNA from serum of all the subjects. The concentration and purity of RNA were tested by Nanodrop™ 2000 spectrophotometer (Thermo Fisher, USA). When the ratio of 260/280 of RNA was between 1.8 and 2.0, it was reverse transcribed to cDNA using the PrimeScript™ RT kit (Takara, Japan). QRT-PCR was conducted using the SYBR PCR Green Master Mix kit (Qiagen, Germany). MiR-134-5p relative abundance was normalized by U6, and calculated using $2^{-\Delta\Delta CT}$. Each reaction was done at least three times.

Ultrasound examination

Color Doppler ultrasound (GE-E8) was conducted to diagnosis of endometriosis, and the probe frequency was set at 4.0-8.0 MHz. The sampling frame was placed on the either side of the junction of the cervix and the uterus, and the uterine arteries crossed at a distance of 1 cm from the external iliac arteries. Stable uterine artery blood flow spectrogram was obtained for three to five consecutive cardiac cycles. Doppler parameters of the uterine arteries were calculated and summarized, including end diastolic velocity (EDV), peak systolic velocity (PSV), resistance index (RI), pulsative index (PI). Each parameter was checked three times, and the average value of three measurements was obtained. All subjects were examined by two sonographers and their assistants using the same ultrasound machine.

Table 1 Basic characteristic information of all the subjects

Characteristics	Endometriosis ($n=119$)	Control ($n=96$)	*P*-value
Age (years)	33.53±5.18	34.61±5.77	0.148
BMI (kg/m^2)	23.03±2.60	22.95±2.25	0.816
Smoking (n, %)	31 (26.05)	22 (22.92)	0.572
Alcohol intake (n, %)	20 (16.81)	16 (16.67)	0.956
Infertility (n, %)	46 (38.66)	32 (33.33)	0.393
Nulliparity (n, %)	25 (21.01)	19 (19.79)	0.802
Dysmenorrhea (n, %)	65 (54.62)	31 (32.29)	0.001
Dyspareunia (n, %)	54 (45.38)	24 (25.00)	0.002
Chronic pelvic pain (n, %)	31 (26.05)	28 (29.17)	0.637
Menstrual disorder (n, %)	28 (23.53)	21 (21.88)	0.748
Cyst size (n, %)			
< 4 cm	78 (65.55)	-	-
≥ 4 cm	41 (34.45)	-	
Cyst location (n, %)			
Unilateral	69 (57.98)	-	-
Bilateral	50 (40.02)	-	
rASRM (n, %)			
I-II	62 (52.10)	-	
III-IV	57 (47.90)	-	

Notes BMI: body mass index; rASRM: revised American Society for Reproductive Medicine; $P<0.05$ means statistical significance

Statistical analysis

SPSS 23.0 (IBM, USA) and GraphPad Prism 9.0 (GraphPad software, USA) were used for the statistical analysis and plotting. G*Power software was used to estimate the sample size for power analysis in two groups, and each group was no less than 90 subjects. Measurement variables of normal distribution were represented as average±SD (standard deviation), and comparisons between two groups were analyzed using Independent Student's t test. The categorical variables were expressed as cases (n) and percentages (%), and the comparison between two groups was analyzed via Chi-square test. Pearson correlation analysis was employed to analyze the correlation of miR-134-5p expression with blood flow Doppler parameters. Receiver operating characteristic (ROC) was adopted to evaluate the diagnostic performance of miR-134-5p combined with indexes. Kaplan-Meier method was conducted to evaluate the recurrence-free survival rate of endometriosis. A *P* value less than 0.05 was set as statistical significance.

Results

Comparative analysis of basic data and characteristics of all subjects

Table 1 listed and compared the general information and characteristics of the endometriosis group and the control group. There was no statistical significance observed between the two groups in age, BMI (body mass index), smoking, alcohol intake, infertility, nulliparity, chronic pelvic pain and menstrual disorder (all $P>0.05$). At the same time, the incidence rates of dysmenorrhea and dyspareunia in endometriosis were 65 (54.62%) and 54 (45.38%), while in the control group, they were 31 (32.29%) and 24 (25.00%), respectively. Compared with the control group, it was found that dysmenorrhea ($P=0.001$) and dyspareunia ($P=0.002$) in patients with endometriosis were remarkably increased. In addition, 62 (52.10%) endometriosis patients were in stage I-II, while 57 (47.90%) patients were in stage III-IV. In the endometriosis group, 78 (65.55%) cases had cysts less than 4 cm, while 41 (34.45%) cases had cysts larger than or equal to

4 cm. 69 (57.98%) cases were unilateral, and 50 (40.02%) were bilateral.

Relative abundances of miR-134-5p expression and values of Doppler parameters in endometriosis patients

In order to examine the expression status of serum miR-134-5p in endometriosis patients, qRT-PCR assay was conducted. Serum levels of miR-134-5p in the control group was 1.156±0.438 in control group, while that in the endometriosis group was 0.723±0.236, suggesting a statistical difference between the two groups ($P<0.001$, Fig. 1A). Subgroup analysis showed that the relative amounts of miR-134-5p were 0.845±0.209 in stages I-II, and 0.590±0.187 in stages III-IV of endometriosis. Compared with patients with endometriosis in stages I-II, a significant reduction was found in patients with endometriosis with stage III-IV ($P<0.001$) (Fig. 1A).

According to Color Doppler ultrasound examination, Doppler parameters of uterine artery blood flow were measured, including EDV, PSV, PI and RI. Values of EDV and PSV were remarkably decreased in endometriosis patients in comparison to the control group, respectively ($P<0.001$, Fig. 1B). On the contrary, a notable increase of PI and RI values was found in endometriosis patients relative to the control group, respectively ($P<0.001$, Fig. 1C).

Correlation analysis serum miR-134-5p with doppler parameters of blood flow in endometriosis patients

In order to analyze the correlation of miR-134-5p and EDV, PSV, PI, and RI, Pearson correlation analysis was carried out. The outcomes suggested that serum miR-134-5p level positively correlated with EDV ($r=0.5777$, $P<0.0001$) and PSV ($r=0.6945$, $P<0.001$), respectively (Fig. 2A-B). However, an adverse correlation was discovered between serum miR-134-5p and PI ($r=-0.6382$, $P<0.0001$) and RI ($r=-0.6247$, $P<0.0001$) in the endometriosis group and the control group (Fig. 2C-D). The results showed that serum miR-134-5p and Doppler parameters were involved in the occurrence and development of endometriosis.

Association analysis between serum miR-134-5p expression and clinicopathological variables in endometriosis sufferers

To further analyze the effect of serum miR-134-5p on the progression of endometriosis, Chi-square was applied to assess the relationship of miR-134-5p and clinicopathological features of endometriosis patients. According to the median value of serum miR-134-5p, patients with endometriosis were classified into two groups: low miR-134-5p expression ($n=66$) and high miR-134-5p expression ($n=53$). It was demonstrated that aberrant miR-134-5p expression was closely related to dysmenorrhea ($P=0.028$), dyspareunia ($P=0.025$) and rASRM stage ($P=0.018$). Nevertheless, no obvious relationship was discovered between serum miR-134-5p and other clinicopathological parameters, such as age, BMI, smoking, alcohol, intake, infertility, nulliparity, chronic pelvic pain, menstrual disorder, cyst size and cyst location (all $P>0.05$) (Table 2).

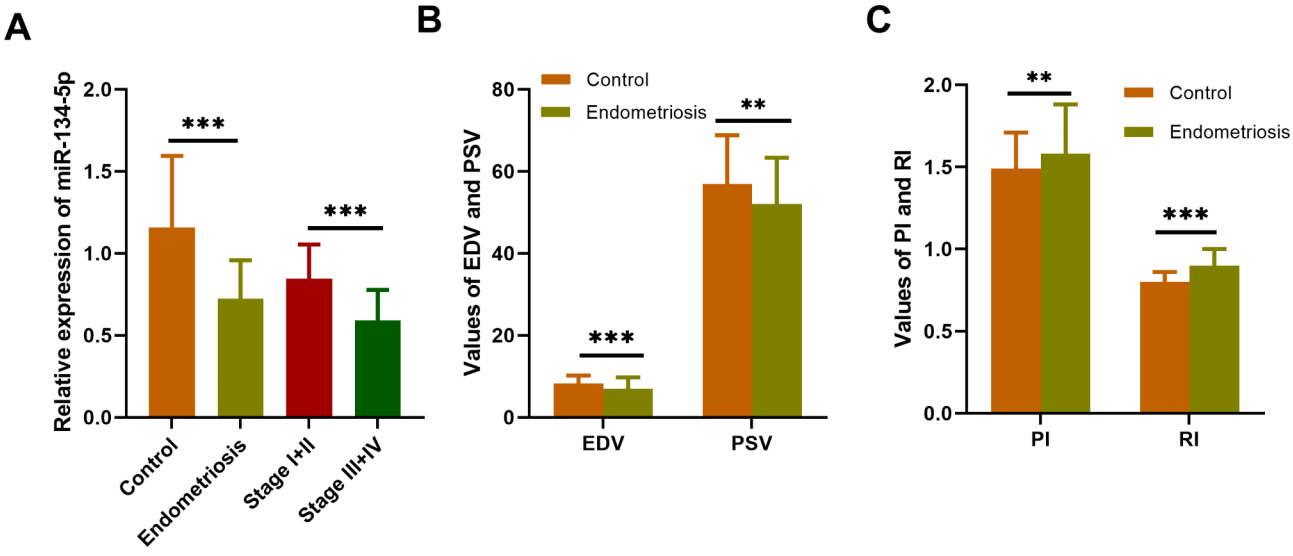

Fig. 1 Relative expression of serum miR-134-5p was examined via qRT-PCR in the endometriosis group and the control group, as well as different stages of endometriosis **(A)**, and values of EDV, PSV **(B)**, PI and RI **(C)** were determined using color Doppler ultrasound in all subjects. Relative to the control group, values of EDV and PSV were significant elevated in endometriosis, while a notable reduction of PI and RI values in was observed. *: $P<0.05$; **: $P<0.01$; ***: $P<0.001$

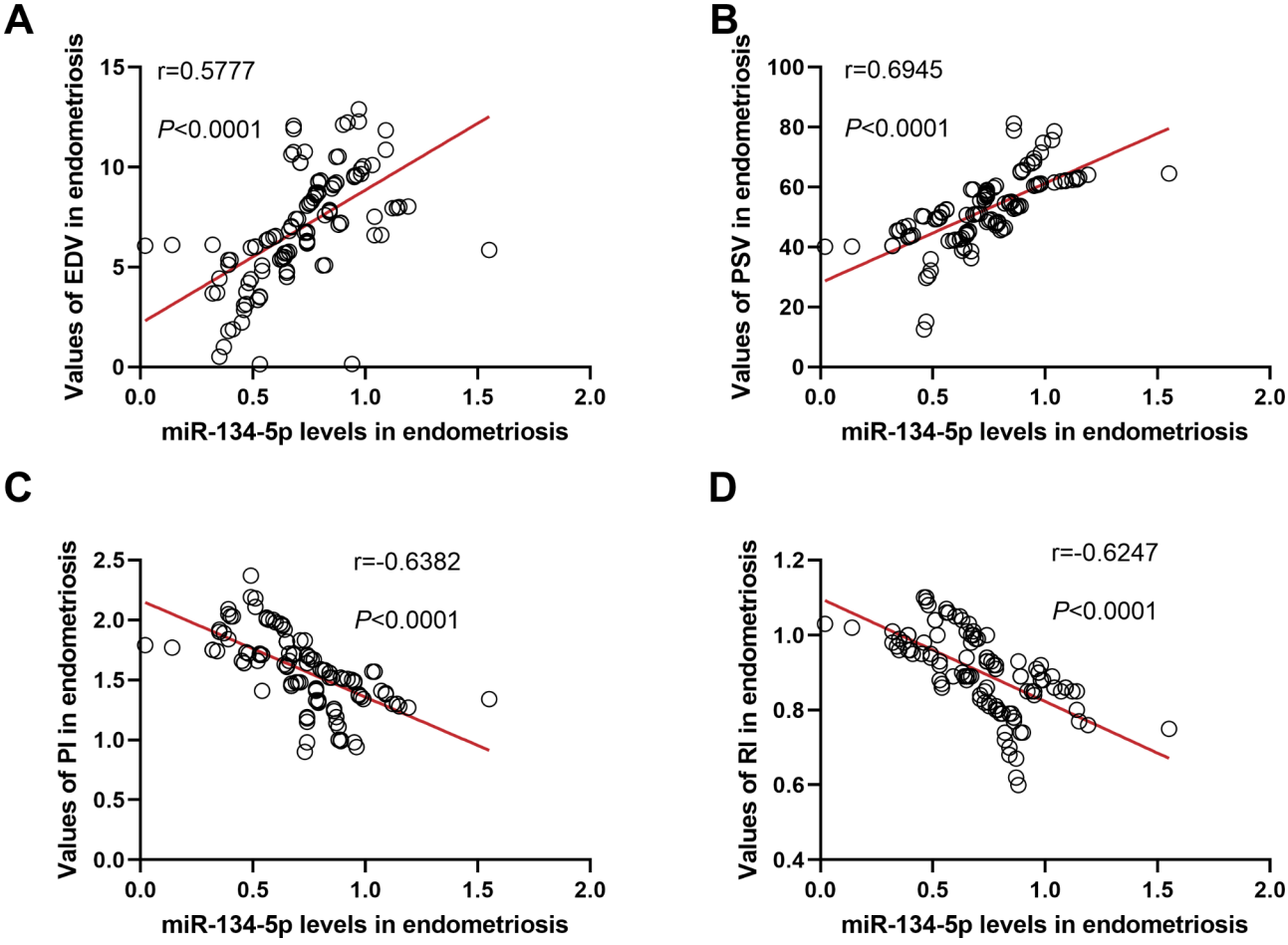

Fig. 2 Correlation analysis of serum miR-134-5p and Doppler parameters of blood flow (EDV, PSV, PI and RI) via Pearson's correlation analysis. Serum miR-134-5p level was positively correlated with EDV ($r=0.5777$, $P<0.001$) **(A)** and PSV ($r=0.6945$, $P<0.01$) **(B)**, respectively. Serum miR-134-5p was adversely correlated with PI (r=-0.6382, $P<0.001$) **(C)** and RI (r=-0.6247, $P<0.001$) **(D)**, respectively

Diagnostic value of serum miR-134-5p and doppler parameters in endometriosis

In order to explore the diagnostic capacity of miR-134-5p and Doppler parameters of the uterine artery in endometriosis, ROC curves were established. The AUC of serum miR-134-5p was 0.822, with the sensitivity of 89.90% and the specificity of 62.50% distinguishing endometriosis patients from patients with gynecological benign diseases, respectively. Moreover, the AUC values of EDV, PSV, PI and RI were 0.652, 0.609, 0.603 and 0.808, respectively, to differentiate patients with endometriosis from gynecological benign diseases (Table 3).

Furthermore, the diagnostic precision of serum miR-134-5p combined with EDV, PSV, PI, RI was also determined. The AUC of the combination diagnosis was 0.905, and the sensitivity of and the specificity of discriminating the endometriosis patients from patients with gynecological benign diseases were 87.40% and 82.29%, which was higher than that of single examination (Fig. 3).

Prognostic significance of miR-134-5p

To further assess the influence of serum miR-134-5p on the progression of endometriosis after operation, the recurrence-free survival rate of endometriosis with 3-year follow up was determined with the Kaplan-Meier method and log-rank test. It was demonstrated that patients with low miR-134-5p expression yielded a shorter recurrence-free survival rate than those with high miR-134-5p (log-rank test $P=0.013$, Fig. 4).

Discussion

As a frequent gynecological disease, the main characteristics of endometriosis are mainly featured by periodic bleeding of the ectopic endothelium and fibrotic changes of the surrounding tissues, leading to ectopic nodules [19]. In spite of being a benign disorder, they have the characteristics of malignant lesions and might affect any organ in the pelvic, thoracic, abdominal, limb or elsewhere in the body [20, 21]. At the early stage, it has no typical features and is very obscure, which is easily

Table 2 Comparison of serum miR-134-5p with clinicopathological features in the endometriosis group

Features	No. (119)	miR-134-5p expression		*P* value
		Low (66)	High (53)	
Age (years)	33.53±5.18	33.62±5.54	33.42±4.73	0.830
BMI (kg/m^2)	23.03±2.60	22.90±2.41	23.19±2.83	0.546
Smoking, n (%)	31	15	16	0.357
Alcohol intake, n (%)	20	9	11	0.302
Infertility	46	22	24	0.183
Nulliparity	25	12	13	0.398
Dysmenorrhea	65	42	23	0.028
Dyspareunia	54	36	18	0.025
Chronic pelvic pain	31	15	16	0.357
Menstrual disorder	28	12	16	0.126
Cyst size				0.500
< 4 cm	78	45	33	
≥ 4 cm	41	21	20	
Cyst location				
Unilateral	69	40	29	0.518
Bilateral	50	26	24	
rASRM, n (%)				
I-II	62	28	34	0.018
III-IV	57	38	19	

Notes BMI: body mass index; rASRM: revised American Society for Reproductive Medicine; *P* < 0.05 means statistical significance

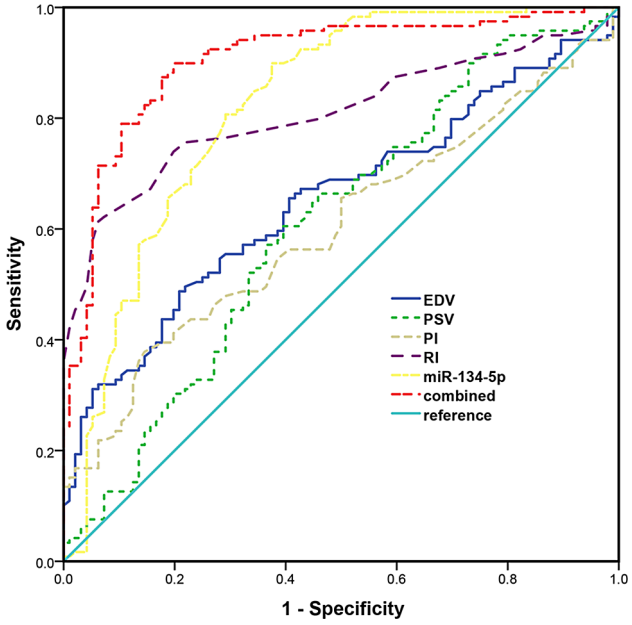

Fig. 3 The diagnostic capacity of serum miR-134-5p combined with values of EDV, PSV, PI and RI to distinguish endometriosis patients from gynecological benign diseases using ROC curves

overlooked by the patients. As the passage of time, the condition began to deteriorate, and the patient missed the best opportunity to receive radical surgery when he was diagnosed. As a gold standard for diagnosis, treatment with laparoscopy could have a significant impact on overall health and psycho-emotional status. In patients with deep infiltrating endometriosis who are insensitive to conventional hormone therapy, diagnostic laparoscopy is considered appropriate to diminish disease progression at an early stage [22]. However, it is invasive and expensive, and its accuracy depends on surgical expertise and technical equipment [23]. Due to the operation itself, the pain symptoms may last or even recur. So, it has limited acceptance by the general public. Early and accurate diagnosis of endometriosis is of great significance for the clarification of the disease, the formulation targeted treatment programs and the improvement of the quality of prognosis.

As an imaging examination method, ultrasound is the first choice for screening endometriosis, which has the advantages of convenient carrying, intuitive observation, high cost performance [24, 25]. Compared with transabdominal ultrasound, the patients don't need to keep their bladder full during transvaginal ultrasound examination, which leads to the reduction of examination time and pain, and is not affected by intestinal air, abdominal fat and abdominal scar. However, relative to gold standard, there is still a certain gap in diagnostic precision of transvaginal ultrasound examination. For example, minor lesions are difficult to find, and there will be missed and misdiagnosed.

In the present study, we used Doppler ultrasound to measure the EDV, PSV, PI and RI values in patients with endometriosis and gynecological benign disease. It was demonstrated that EDV and PSV are significantly decreased in endometriosis patients compared with gynecological benign disease. In the contrast, remarkably increased values of PI and RI were found in patients with

Table 3 Diagnostic value of EDV, PSV, PI, RI and miR-134-5p

Parameters	Sensitivity	Specificity	AUC	Cut-off	*P*-value	95%CI
EDV / (cm/s)	48.70	79.17	0.652	6.725	< 0.001	0.579–0.725
PSV / (cm/s)	60.50	60.42	0.609	53.805	0.006	0.533–0.685
PI	37.80	85. 42	0.603	1.695	0.010	0.528–0.678
RI	61.30	93.75	0.808	0.875	< 0.001	0.750–0.867
miR-134-5p	89.90	62.50	0.822	1.000	< 0.001	0.763–0.881
Combined	87.40	82.29	0.905	-	< 0.001	0.863–0.947

Notes EDV: end diastolic velocity; PSV: peak systolic velocity; PI: pulsative index; PI: resistive index; miR-134-5p: microRNA-134-5p; AUC: the area under curve; 95%CI: confidence internal; *P* < 0.05 means significant difference

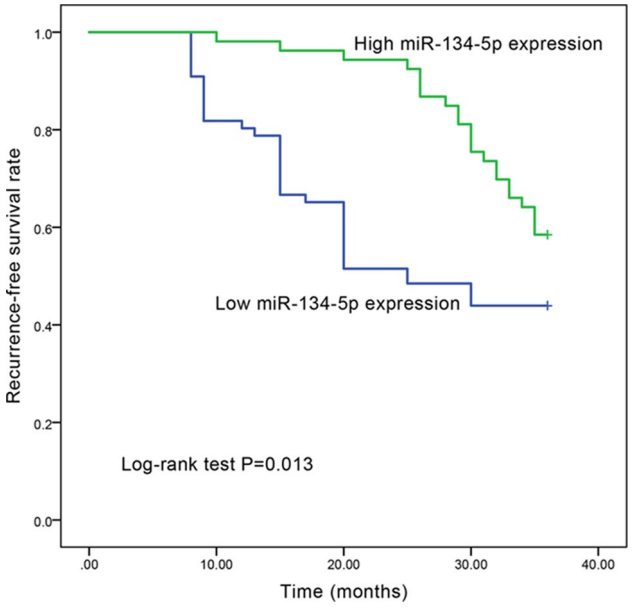

Fig. 4 The predictive performance of serum miR-134-5p in prognosticating the recurrence of endometriosis via Kaplan-Meier method and log-rank test. The recurrence-free survival rate in patients with low miR-134-5p expression was lower than those with high miR-134-5p expression ($P=0.013$)

endometriosis. It was indicated that Doppler parameters of uterine artery blood flow might be related to the formation of endometriosis.

Serum biomarkers have become a pivotal method for the diagnosis of many diseases because biomarker testing has many advantages, including safety and convenience, which might be a useful aid to laparoscopic exploration in clinical practice. MiRNAs can participate in cellular behaviors such as cell proliferation, differentiation, migration and apoptosis of human diseases by targeting the translation-inhibited or degraded mRNAs. Most articles have reported that miRNAs play important roles in the initiation and formation of gynecological disorders, including endometriosis. A paper reported by Walasik and others showed that plasma miR-3613-5p had a distinctly reduced level in endometriosis, displaying a high diagnostic value [26]. On the other hand, the serum samples of endometriosis showed a decrease in the level of miR-34a-5p and an increase in the level of miR-200c, which showed the potential diagnostic performance of the disease [27]. As a promising miRNA, miR-134-5p has be reported to be related to the initiation and formation of gynecological disorders, such as ovarian cancer and endometriosis. For instance, in ovarian cancer, miR-134-5p was obviously diminished in ovarian cancer cell lines and participated in progression in tumor development [28, 29]. Moreover, Zhang and others elucidated that the down-regulation of miR-134-5p in endometriosis was clarified by via microarray analysis [30]. Nevertheless, little is knwon about the diagnostic performance of serum miR-134-5p in endometriosis.

In the present study, the relative abundance of miR-134-5p in serum specimens of the study group and the control group was detected by qRT-PCR assay. The results showed that the expression level of miR-134-5p in serum of patients attacked by endometriosis decreased significantly. Additionally, the relationship of miR-134-5p with clinicopathological factors was also analyzed. The results showed that aberrant miR-134-5p levels were notably in relation to dysmenorrhea, dyspareunia and rASRM stage, which indicated that aberrant miR-134-5p expression could be associated with the occurrence and formation of endometriosis. Furthermore, the correlation analysis between miR-134-5p and EDV, PSV, PI and RI values was performed, which proved demonstrating that a positive correlation was observed between serum miR-134-5p and values of EDV and PSV, respectively, while an adverse correlation in serum miR-134-5p and values of PI and RI, respectively, was observed. More importantly, diagnostic accuracy of miR-134-5p and EDV, PSV, PI and RI values was determined via establishing ROC curves. It was revealed that the combination diagnosis of serum miR-134-5p and transvaginal Doppler parameters displayed a higher sensitivity and specificity than those of single examination.

A few shortcomings should be pointed out, although the results from our preliminary experiment are promising. This study is retrospective research with limited data, small sample size and single source, so they may introduce a certain degree of deviation in the results. Therefore, we also need to carry out multi-center and larger-sample prospective study to evaluate the stability and reliability of the experimental results.

Taken together, serum miR-134-5p levels in endometriosis were distinctly different, and it is closely related to the Doppler parameters of uterine artery blood flow. The diagnostic performance of serum miR-134-5p combined with Doppler ultrasound is superior to each single index, indicating that the combined diagnosis of endometriosis has a potential diagnostic value.

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Author contributions
Conceptualization, S.J., X.S., J.L. and T.W.; Data curation, S.J., Z.X., J.L. and M.L.; Formal analysis, Z.X., M.L. and L.B.; Funding acquisition, X.S. and T.W.; Investigation, S.J., X.S., M.L. and L.B.; Methodology, J.L. S.J., X.S.; Project administration, X.S. and T.W.; Resources, M.L. and L.B.; Software, M.L. and L.B.; Supervision, X.S. and T.W.; Validation, M.L. and L.B.; Visualization, J.L.; Roles/Writing - original draft, S.J., X.S., X.S. and J.L.; Writing - review & editing, X.S. and T.W.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The Second Affiliated Hospital, School of Medicine, The Chinese University of Hong Kong before the study began. The participants' right to be informed about the study was ensured and agreed to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Ultrasound, Tianjin Central Hospital of Gynecology Obstetrics, Tianjin 300199, China
[2]Department of Gynecology and Obstetrics, The First Hospital of Jilin University, Changchun, China130000
[3]Department of Ultrasound Medicine, The Second Affiliated Hospital, School of Medicine, The Chinese University of Hong Kong, No.53, Aixin Road, Longcheng Street, Longgang District, Shenzhen, Guangdong 518172, China
[4]Health Management Center, The Second Affiliated Hospital, School of Medicine, The Chinese University of Hong Kong, Shenzhen 518172, China
[5]Department of Ultrasound Medicine, Nanhai District Maternity & Child Healthcare Hospital, Foshan 528299, China
[6]Department of Gynecology, Nanjing JiangNing Hospital of Chinese Medicine, Tianyin Avenue 657, Jiangning District, Nanjing 211100, China

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