Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i18.3361

IMMUNOLOGICAL BIOMARKERS AND PROGNOSIS OF ENDOMETRIAL CANCER: A META-ANALYSIS

Emama Arshad Abbasi[1], Nisha Hamid Awan[2], Soffia Khursheed[3], Sohail Ahmed[4], Jahanzeb Ahmed[5], Amna Akbar[6*], Sabahat Tasneem[7], Mohammad Saleem khan[8], Sarosh Khan Jadoon[9]

[1]Houseofficer, Combined Military Hospital, Muzaffarabad, AJK, Pakistan, arshademama26@gmail.com
[2]Resident Medicine, Combined Military Hospital, Muzaffarabad, AJK, Pakistan, nishahamidawan@gmail.com
[3]Assistant Professor Histopathology, Pakistan Institute of Medical Science, Islamabad, Pakistan, soffiakhursheed@gmail.com, https://orcid.org/0009-0005-2156-1418
[4]Post Graduate Student, Yangtze University, Hubei province, Jingzhou, China, sohail2050@proton.me
[5]Trainee General Surgery, Department of Gastrointestinal Surgery, Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, Chinajahanzebahmed@163.com
[6*]Medical Officer, District Headquarter Hospital Jhelum Valley, AJK, Pakistan, amna.akbar1324@gmail.com, https://orcid.org/0009-0009-6560-5493
[7]Public Health Professional (MSPH), Health Services Academy, Islamabad, Pakistan, tasneem.saba30@gmail.com, https://orcid.org/0009-0004-4947-8213
[8]FRCP(Glasgow), FRCP(Edin), FRCP (Ireland), FACP, FPSIM, FCPS, MCPS, MBBS (Gold Medallist), Chief Consultant Physician /Head of Department of Medicine DHQ Teaching Hospital Kotli AJK, Pakistan, dr.moh.saleem@gmail.com
[9]Resident Surgeon, Combined Military Hospital, Muzaffarabad, AJK, Pakistan,saroshkhanjadoon@outlook.com, https://orcid.org/0000-0002-1728-2599

***Corresponding author:** Amna Akbar
*Medical Officer, District Headquarter Hospital, Jhelum Valley, AJK, Pakistan
amna.akbar1324@gmail.com, https://orcid.org/0009-0009-6560-5493

Abstract

Objective: This research is to explore the relationship in immune related biomarkers and prognosis in endometrial cancer (EC).

Method: This article searched relevant databases and literature, and ultimately included 13 articles for meta-analysis. During the literature screening process, irrelevant literature, as well as literature published in comments and academic conferences were excluded. Among the included literature, there are 6 articles related to miR-421 and 7 articles related to miR-548ag. The data processing of Meta-analysis adopts statistical methods.

Result: The combined specificity and SROC curve results of meta-analysis showed that miR-421 and miR-548ag possess high diagnostic value for EC. At the same time, sensitivity analysis was conducted on the overall survival rate of OS, and no significant impact was found on combined HR and 95% CI

in any study. This indicates that miR-421 and miR-548a possess an essential influence on the prognosis of EC and demonstrates the reliability of this analysis.

Conclusion: The relevant outcomes suggest that miR-421 and miR-548ag may be biomarkers for the prognosis of endometrial cancer. These findings have important guiding significance for a deeper understanding of the pathogenesis, pathological and physiological changes, and clinical treatment of endometrial cancer. It is essential to conduct more research for validating the role of these biomarkers in the prognosis of endometrial cancer.

Keywords: Endometrial Cancer; miR-421; miR-548ag; Biomarkers; Meta Analysis

Introduction

Endometrial carcinoma (EC) is a type of tumour with the endometrium as the main pathological type, also known as uterine body tumour, and is a common gynaecological malignancy. According to the 2021 American Cancer Report, the incidence rate and mortality of EC among women rank fourth and sixth respectively. In China, EC is a common malignant tumour, and its incidence rate ranks eighth among women [1]. In recent years, the incidence rate and mortality of EC are on the rise, and there is a trend of youth, which poses a great threat for women's health. Although early diagnosis, surgery, radiotherapy, and chemotherapy are important methods to improve its efficacy, for early lesions, fertility needs to be preserved, and the efficacy is still not ideal for women with advanced or recurrent diseases.

EC is separated into type I and type II in view of its pathogenesis, with type I EC being more associated with obesity. In recent years, the worldwide incidence rate of overweight (WHO BMI>25 kg/m2) and tumour burden have been rising. Previous studies have shown that the incidence of EC is closely related to age (>60 years old), but this feature changes with the increase in the number of obese women, and the age of EC incidence is younger [2]. A set of data consisting of seven prospective studies shows that for every five units increase in body mass index between the ages of 18 and 25, the risk of developing EC increases by 42%. In recent years, with the continuous discovery of various adipogenic factors, people have gradually realized that fat is not only an energy storage organ, but also a substance with endocrine effects. Atakul et al. found that adipose tissue is an important storage site for microRNAs derived from exosomes. Exosomes are tissue specific microRNAs secreted by different tissues, which can enter various tissues with blood flow and affect the body's function by regulating the expression of target genes [4]. MiRNAs are a class of 22 base long single strand non-coding RNA that can bind to the target gene 3'UTR, degrade its mRNA, and regulate the expression of a variety of tumour related genes at the post transcriptional level.

The studies in the past have discovered that miR-421 and miR-548ag are highly expressed in EC and knocking them down can significantly inhibit the proliferation of EC [5]. In recent years, miR-421 and miR-548ag have been widely reported by scholars both domestically and internationally as important functions of miRNA in EC. Therefore, this project is for investigating the role of miR-421/miR-548ag in tumour diagnosis. A single study may not be sufficient for obtaining a complete conclusion. Therefore, this project aims to integrate meta-analysis for clarifying the correlation in miR-421/548ag and the occurrence, development, and prognosis of EC.

2. Materials and Methods

2.1 Retrieval Strategy

Meta-analysis (MA) is conducted in accordance with the principles stated in the "List of Preferred Reports on System Assessment and MA" (PRISMA) [6]. By searching common Chinese and English literature such as public, Embase, WSF Science, CNKI, Wan fang Database, and VIP, we obtained literature on the diagnostic and prognostic value of miR-421 and miR-548ag in EC patients (the most recent search was on May 4, 2023). The corresponding keywords are: "miR-421", "miR-548ag", "miRNA-421", "miRNA-548ag", "EC", "endometrial cancer" (miR-421, miR-548ag); It randomly places topic words and space words together to ensure the most comprehensive information. In

addition, in order to identify the neglected relevant literature, a list of references also is carried, MA, and manual search of all original literature.

2.2 Inclusion and Exclusion Criteria

To select trials meeting the requirements, the inclusion criteria for this trial are as follows: (1) The subjects of this trial are confirmed EC patients; (2) The expression of miR-421 and miR-548ag in tumour tissue and circulation; (3) Evaluate the relationship between poor prognosis and diagnostic accuracy of miR-421 and miR-548ag in EC patients.

In addition, the exclusion conditions include: (1) the sample is completely consistent with the sample used in the published document; (2) Non-Chinese or non-English documents; (3) Incomplete or non-compliant information; (4) The overall survival rate is not used as a prognostic indicator.

2.3 Data Extraction

After removing repetitive literature, two independent researchers screened the searched literature for titles and abstracts based on existing entry and exit criteria. On this basis, we selected the literature by reading literature that may meet the criteria. According to the information required in the selected literature, after discussion and consensus with another researcher, the uncertain results were extracted again. The extracted data included these contents: (1) Research characteristics: the name of the lead author, publication time, and country; (2) Characteristics of the tested substance: miRNAs type, tumour grade, sample type; (3) Relevant data required for meta-analysis: To conduct diagnostic meta-analysis, 2x2 data tables were selected, including SEN (sensitivity), SPE (specificity), ROC (area under ROC curve), FN (TN), TN, TP, FP, etc. Meta method was used to analyse the prognostic indicators, HR values, overall survival rate (OS), and 95% confidence interval (CNI) (95% CNI) of patients. For data that cannot be directly reported, this project will utilize the HR values and 95% CNI based on the Kaplan Meier curve proposed by Engage Digitizer 4.1 and Tierney et al.

2.4 Quality Assessment

Two researchers estimated the quality of each paper using their respective quality evaluation tools. However, when two researchers have different opinions, the other researcher reevaluated the results and ultimately reach a consistent result. For diagnostic meta-analysis, the QUADAS-2 (Quality Association Research Quality Assessment) guidelines were used [7]. On this basis, this research is for evaluating the applicability and bias risk of clinical diagnostic research, divided into categories (7 items in total): patient selection (2 items), indicator testing (2 items), and reference standards (2 items), and process and time limit (1 item). In terms of clinical prognosis, the Newcastle Ottawa Scale (NOS) is utilized for evaluating the patient's prognosis. The NOS score includes: ① selection and definition of research subjects (0-4 points); (II) Comparability between groups of the same category (0-2); (III) Judgment score (0-3); The possible scoring range for each experiment is 0 to 9, while experiments with a NOS score exceeding 7 are considered high-quality experiments.

2.5 Statistical Analysis

MA was carried in view of STATA15.0 and Review Manager 5.3. It uses Cochran's Q and Weighted Statistics indicators to evaluate heterogeneity in various studies. If $p>0.1$ and $I<50\%$, then it indicates that the included research satisfies homogeneity; If $p<0.1$ and $I>50\%$, then it demonstrates significant heterogeneity.

In diagnostic meta-analysis, we use a binary mixed effect regression model to integrate various diagnostic indicators. It evaluates the threshold effect between each diagnostic group using the receiver operating curve (ROC) and Spearman correlation analysis method. On the ROC curve, a strong positive relation existing the sensitive logarithm and the 1-specific logarithm; indicating the threshold effect. On this basis, it calculates the sensitivity, specificity, and corresponding 95% CI of each indicator to obtain the area under the curve (AUC) of the total subject's working curve and draws the corresponding "forest" map. The AUC value varies between 0.5 and 1.0, and when the AUC value approaches 0.5, it indicates poor detection performance; When AUC is around 1.0, it shows good

diagnostic performance. Meanwhile, a subgroup analysis method was used to explore the influencing factors. For evaluating the application value of miR-421 and miR-548 ag in early diagnosis of EC through subgroup analysis of circulating samples (serum, plasma, cerebrospinal fluid). Using Deeks' funnel chart as an evaluation indicator for publication bias (α) 0.05 is used as the evaluation indicator, with $p<0.05$ as the significant difference (SD).

It evaluates the prognostic value of miR-421 and miR-548ag in EC through meta-analysis. This study used high expression miR-421 and miR-548ag as controls (HR=1), and low expression miR-421 and miR-548ag as controls. Patients with high expression of miR-421 and miR-548ag have poor prognosis. If there are differences between samples ($p<0.10$, $I>50\%$), a random effects model will be utilized for statistically analysing the differences between samples ($p<0.10$, $I>50\%$); On the contrary, a fixed effects model is utilized. Meanwhile, through subgroup analysis of countries, tumour levels, and sample sources, identify the root causes of heterogeneity. On this basis, the stability of the included studies is evaluated by removing them item by item and combining them with the clinical outcome indicator OS to determine whether they have good stability. Otherwise, it is considered poor. Finally, the publication bias was tested through funnel plots, Bayesian and Ehrlich tests. Adopting $\alpha < 0.05$, $p<0.05$ illustrates a dramatic disparity.

3. Results and Discussion

3.1 Literature inclusion results

This study searched for a total of 1256 articles related to miR-421, miR-548ag, and EC through Chinese and English databases and other resources. At first, 459 papers were deleted due to duplication. Secondly, 724 papers that were not related to this topic and 34 papers published in comments and academic conferences were removed from the paper title and abstract. On this basis, we evaluated the remaining 40 papers. Through the evaluation of these papers, we excluded 14 papers that were not related to the diagnosis and prognosis of the disease, 8 papers that did not have a primary outcome and 1 paper that did not obtain data. Finally, a total of 31 studies from 16 articles were involved in the MA. This study included 16 references, 6 involving miR-421, 7 involving miR-548ag, and 3 involving both miR-421 and miR-548ag. The relevant process is indicated in Figure 1.

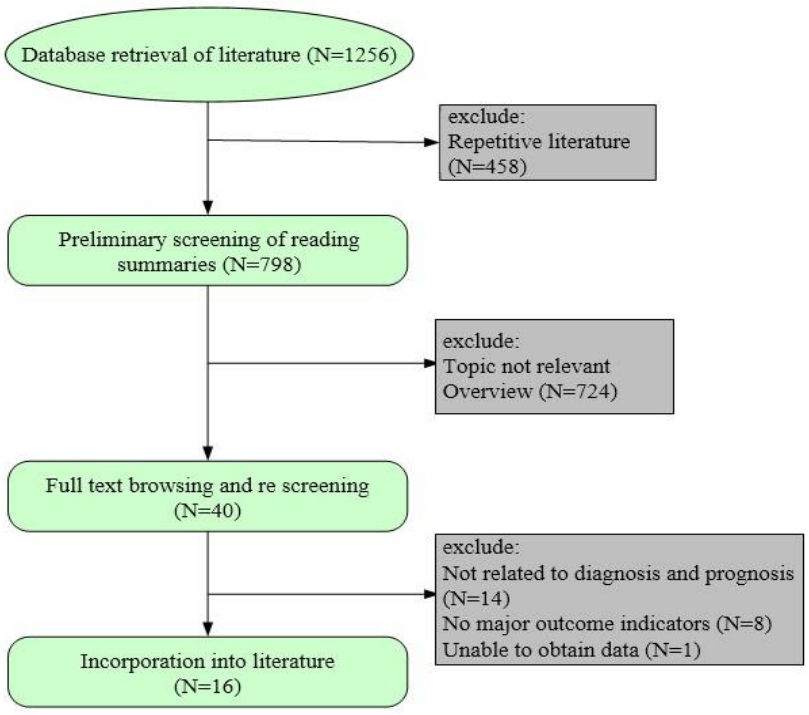


Figure 1 Literature inclusion process

3.2 Diagnostic Meta Analysis

3.2.1 Research Characteristics and Quality Assessment

A total of 8 articles and 13 studies were collected for diagnostic meta-analysis in this study, with 3 articles reporting miR-421 and miR-548ag, respectively. The enrolment period was from 2013 to 2023, with a sample of 15-60 people. According to the World Health Organization (WHO) classification, EC was classified as type I and type II. The sample types are serum, CSF, and tumour tissue. Among them, 6 studies targeted miR-421 and 7 articles analysed miR-548ag. In addition, all included trials were scored using QUADAS-2 and the results of quality evaluation were displayed, as shown in Figure 2.

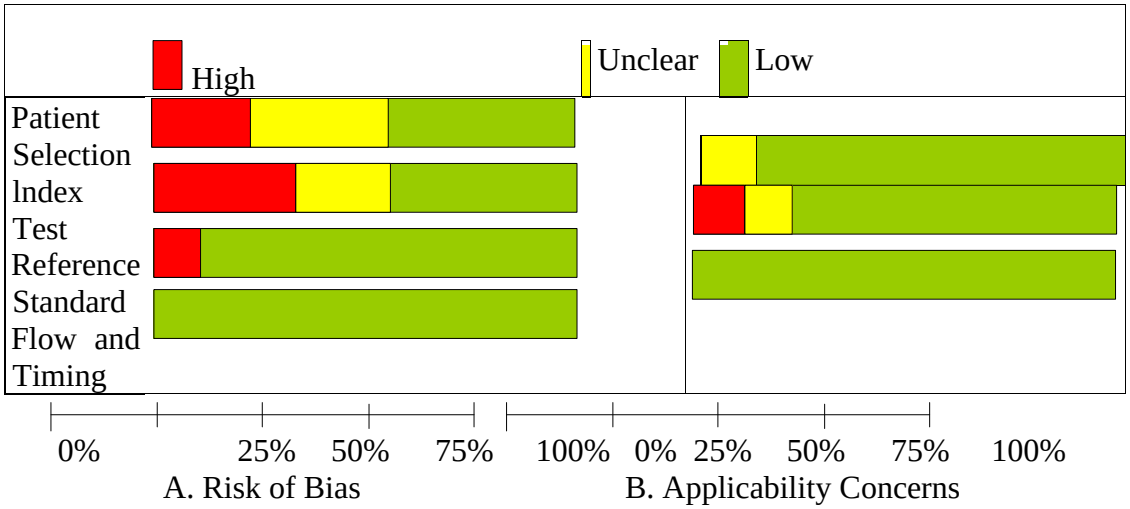
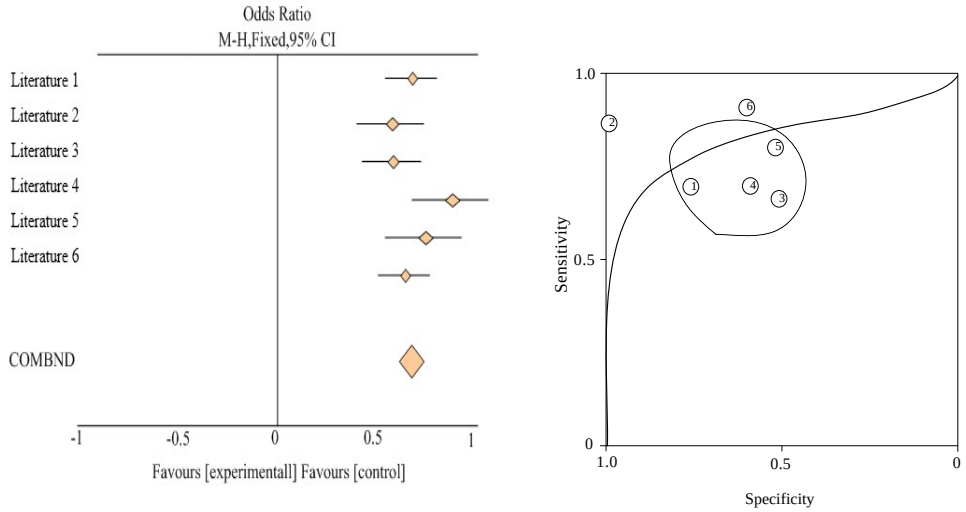


Figure 2 QUADAS-2 Scoring

3.2.2 Comprehensive diagnostic value of miR-421 in EC (1) Statistical results



A specific forest map B SROC curve

Figure 3 Comprehensive diagnostic value of miR-421 in EC

Figure 3A shows a joint specificity of 0.75 (95% CI: 0.65-0.83). Meanwhile, from the SROC curve shown in Figure 3B, the AUC value was calculated to be 0.83 (95% CI: 0.79-0.86). The above results suggest that miR-421 has high diagnostic value for EC.

(2) Heterogeneity and subgroup analysis

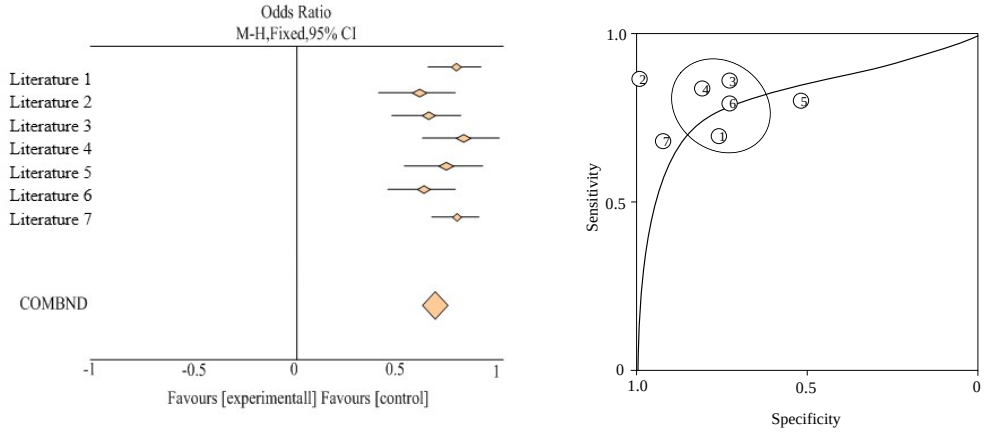
There are varying degrees of differences between different studies. A correlation analysis was conducted on 6 references, and the specificity of the results was 0.143, with a p-value of 0.787. The application of the Western Statistics index (p=35.01%, I^2=56.99%) suggests varying degrees of heterogeneity in this study.

To further explore its heterogeneity and due to the limited number of samples, this project only analyses samples sourced from China, including peripheral blood (serum, plasma, and cerebrospinal fluid) and peripheral blood (cerebrospinal fluid). The results showed that there were 4 articles in China, with a comprehensive sensitivity of 0.76 (95% CI: 0.68-0.82) and I^2=35.94%; The specificity is 0.72 (95% CI: 0.65-0.79). The heterogeneity between subgroups of the study subjects from China was significantly reduced, indicating that the differences between the study subjects largely depend on the differences between patients in this study.

3.2.3 Comprehensive diagnostic value of miR-548ag in EC

(1) Statistical results

In Figure 4A, the synthetic sensitivity is 0.79 (95% CI: 0.71-0.85); From the SROC curve shown in Figure 4B, the AUC value was calculated to be 0.89 (95% CI: 0.86~0.92). The above results are like miR-421, indicating that miR-548ag also has high clinical application value for EC.



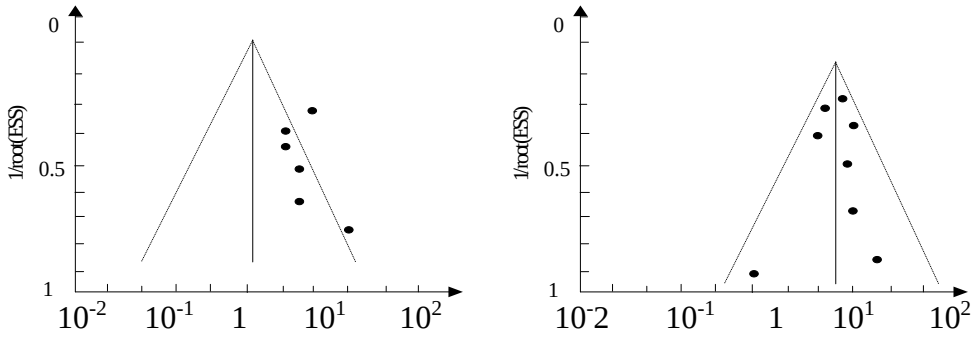
A specific forest map B SROC curve

Figure 4 Comprehensive diagnostic value of miR-548ag in EC

(2) Heterogeneity and subgroup analysis

According to statistics, the Spearman correlation coefficient of 7 diagnostic studies was -0.143, with a p-value of 0.760, indicating high heterogeneity between the two groups. On this basis, subgroup analysis was conducted based on regions, samples, etc. to determine the differences between different samples. The results showed that there were 4 articles in China, with a comprehensive sensitivity of 0.83 (95% CI 0.77-0.88) and I^2=0. The specificity is 0. (95% CI: 0.76~0.87), and I^2=0. The AUC value is 0.9,95% CI: 0.87-1.0. Subgroup analysis is like miR-421, but the differences in the Chinese population are relatively small, indicating that this heterogeneity is likely to originate between different populations.

3.2.4 Bias analysis



A. miR-421 B. miR-548ag

Figure 5 Funnel diagram of miR-421 and miR-548ag in EC diagnosis

We used the Deeks' funnel plot for meta-analysis to evaluate publication bias and found that there was publication bias between miR-421 groups (p=0.04); In miR-548ag, the funnel plot of Deeks was basically symmetrically distributed, and no significant publication bias was found (p=0.96), as shown in Figure 5.

3.3 Meta analysis of prognosis

3.3.1 Research Characteristics and Quality Assessment: In this project, we collected 11 literature and 18 studies, of which 6 reported both miR-421 and miR-548ag. In addition, there are 3 articles and 6 studies based on sample data from the care genome atlas (TCGA). The enrolment time span is from 2011 to 2023, and EC is classified into Class I and Class II according to World Health Organization standards. This project uses the Newcastle Ottawa Securities (NOS) scale for evaluating the selected prognostic studies, with a score of 7-9 being high-quality studies.

3.3.2 Comprehensive prognostic value of miR-421 in EC

(1) Statistical results

Due to the high heterogeneity of 10 studies on OS (I^2=75.70%, p<0.001), a random effects model is utilized for synthesizing the influencing factors. Research has found that high expression of miR-421 in EC is positively correlated with OS, as shown in Figure 6.

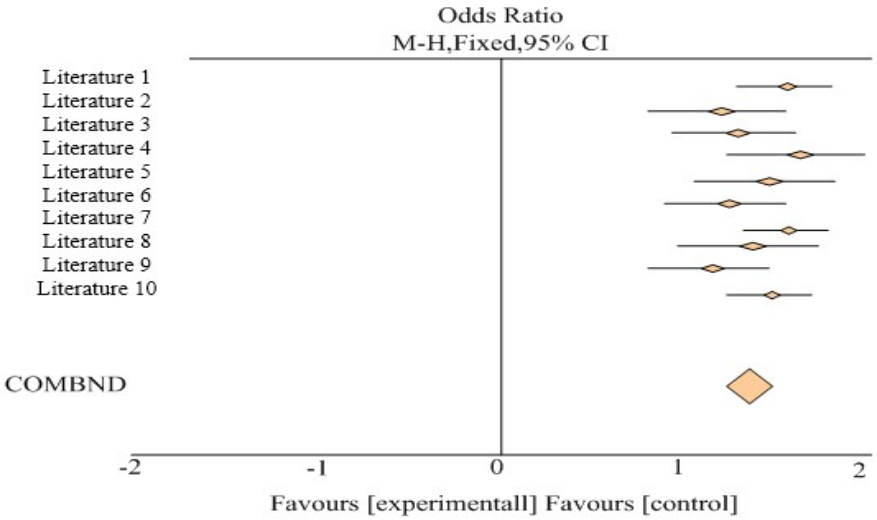


Figure 6 Forest map of overall survival OS in patients with miR-421 overexpression

(2) Heterogeneity and subgroup analysis: This study conducted an in-depth analysis of heterogeneity, comparing subgroup differences between different studies (75.70%, p<0.001), and combining clinical data analysis to elucidate the impact of differences between different studies (patient source, tumour type, sample type) on the overall survival OS of EC patients. We divided this result into subgroup analysis. Table 1 shows that the analysis of subgroups from the patient's country of origin showed a significant reduction in this difference in the Chinese subgroup, with I^2=0% and p=0.632. A comparison was made between different levels of subgroups, and it was found that heterogeneity was significantly reduced in different types of EC patients, with I^2=0% (p=0.432). The subgroup analysis score of the sample type indicated a dramatic decrease in heterogeneity in the subgroup of tumour tissue, with I^2=0% (p=0.714). This indicates that patient origin, tumour grade, and sample type are important factors leading to tumour heterogeneity.

3.3.3 Comprehensive prognostic value of miR-548ag in EC

(1) Statistical results: There is a SD in the prognosis in miR-548ag and EC patients (p<0.05, I^2=65.90%). Therefore, miR-548ag is compared with the prognosis of EC patients utilizing a random

effects model and found that miR-548ag is relevant to the prognosis of EC patients, as shown in Figure 7.

Table 1 Subgroup analysis of overall survival OS in patients with miR-421 overexpression

Research subgroup	classification	Number of studies	HR (95% CI)	p-value	Heterogeneity detection	
					I^2	p-value
Country	China	8	1.86 (1.42,2.19)	<0.001	0%	0.632
	Other	2	1.37 (1.01,1.96)	0.856	86.3%	<0.001
EC type	type I	7	1.79 (1.41,2.41)	<0.001	0%	0.432
	Type II	3	1.09 (0.65,1.76)	0.756	84.3%	<0.001
Specimen type	Serum	2	2.56 (1.57,4.06)	<0.001	0%	0.487
	Tumour tissue	5	1.71 (1.31,2.24)	<0.001	0%	0.714
	TCGA	3	0.78 (0.39,1.48)	0.39	89.1%	<0.001

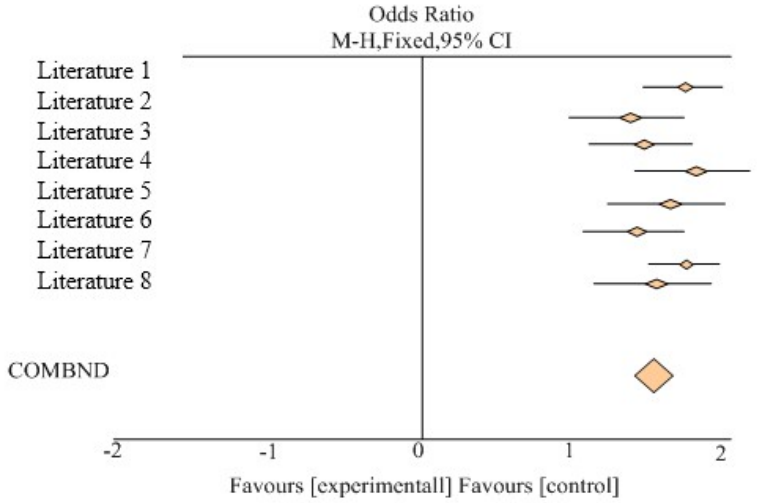


Figure 7 Forest map of overall survival OS in patients with high expression of miR-548ag

(2)Heterogeneity and subgroup analysis

This project aims to use miR-548ag as a starting point to conduct subgroup analysis of miR-548ag from patient sources, tumour grading, and sample types to identify the root causes of heterogeneity. The relevant outcomes are shown in Table 2. The difference from the miR-421 group is that only the sample type subgroup analysis showed a more significant decrease in heterogeneity, while no significant decrease in heterogeneity was found in the analysis of patient origin and tumour level. The above results suggest that different sample types may possess an essential influence on different studies.

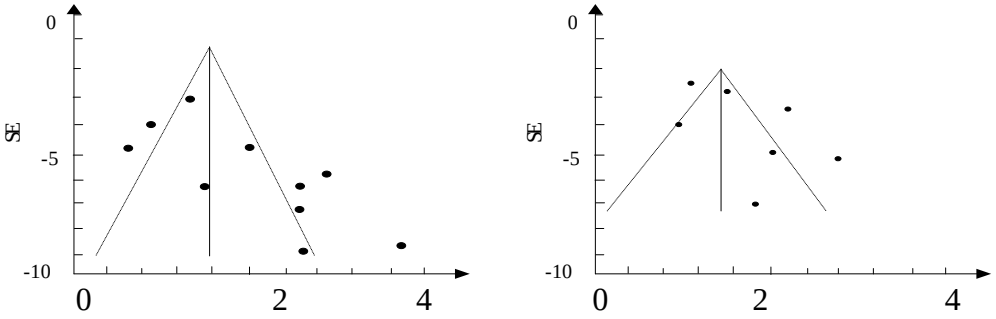
Table 2 Subgroup analysis of overall survival OS in patients with high expression of miR-548ag

Research subgroup	classification	Number of studies	HR (95% CI)	p-value	Heterogeneity detection	
					I^2	p-value
Country	China	6	1.82 (1.02,3.19)	0.038	68.8%	0.023
	Other	2	1.52 (1.21,1.92)	<0.001	68.8%	0.023
EC type	Type I	3	2.58 (1.68,3.92)	<0.001	0%	0.534
	Type II	5	1.44 (1.17,1.76)	0.001	65.8%	0.021
Specimen type	Serum	2	2.73 (1.67,4.46)	<0.001	0%	0.706
	Tumour tissue	3	1.48 (0.86,2.53)	0.177	44.8%	0.163
	TCGA	3	1.52 (1.32,1.78)	<0.001	78.8%	0.009

3.3.4 Publication bias

The funnel plots of miR-421 and miR-548ag are shown in Figures 8A and 8B, respectively, with poor symmetry. However, due to the limited length of this article, it is difficult to make an accurate judgment on the publication bias of this meta-analysis from the perspective of a "funnel plot" only. It

then analyses publication bias using Bayesian and Ehrlich tests. In the analysis of miR-421, the results of Begg's test were 0.474 and Egger's test were 0.564, indicating no published bias between the two groups.



A. miR-421 B. miR-548ag

Figure 8 Funnel plots of miR-421 and miR-548ag in EC prognosis

The statistical values of miR-548ag were 0.902 and 0.182, respectively. The relevant outcomes reveal that the data presented in this study are reliable in the meta-analysis of prognosis.

Discussion

In recent years, with the increase of obesity worldwide, the incidence rate of EC is also on the rise. Type I EC is closely related to obesity and its pathogenesis is still unclear. Studies have discovered that relative to the normal relevant group, EC patients have markedly higher body mass index (BMI), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and glutamate (GLU) [8]. However, the molecular mechanism underlying the progression of EC caused by obesity is still unclear. In recent years, domestic and foreign scholars have compared the miRNAs expression profiles of EC patients and normal individuals to screen miRNAs that can be used for early diagnosis of EC. Among them, miR-421/miR-548ag is a potential EC molecular marker. MiRNAs serve as a class of non-coding small RNAs with negative regulatory functions. Fat is the most important storage site for circulating microRNAs in the body, which possess an essential influence on the occurrence and development (OAD) of major diseases like metabolic disorders, inflammation, and tumours caused by obesity. Reports have shown that overexpression of hsa-miR-421 in gastric cancer can promote invasion and metastasis, inhibit apoptosis, and induce chemotherapy resistance in vitro and in vivo [9]. Hsa-miR-421 can target the regulation of PDCD4 (programmed cell death 4) expression, thereby affecting the proliferation, migration, and S-phase arrest of HCC (hepatocellular carcinoma) cells, suggesting that hsa-miR-421 may become a new target for the diagnosis and treatment of HCC [10]. Further research has found that hsa-miR-421 significantly inhibits the OAD of colorectal cancer by regulating its downstream target gene MTA1 [11]. Previous studies by J Rubio P é rez et al. found that hsa-miR-421 can markedly enhance the proliferation ability of head and neck tumour cells, while inhibiting tumour cell apoptosis, illustrating that it is a potential oncogene [12]. Previous studies have found that hsa-miR-421 can markedly inhibit the proliferation and apoptosis of PCA cells, indicating its anti-cancer function [13]. Some scholars have discovered that hsa-miR-421 is low expressed in ovarian cancer tissues and metastatic cell lines, and is closely related to lymph node metastasis, recurrence, and TNM staging. Moreover, its low expression in ovarian cancer suggests that it may play an anti-tumour role [14]. The above results suggest that there may be differences in the function of hsa-miR-421 in tumours. This project will be the first to confirm has-internationally_ circ_ 0011324 interacts with hsa-miR-421, and through its regulation of SPOCD1, elucidates the molecular mechanism of circRNA, ceRNA, mRNA in the occurrence and advancement of endometrial cancer, providing a theoretical basis for searching for new therapeutic targets. There are literature reports that miR-200c can exert anti-tumour effects by regulating the STAT3-G9a pathway [15]. MiR-31 can inhibit the fat synthesis of breast cancer cells, thereby affecting the growth and migration of tumour cells. However, the role of miR-302a-5p/367-3 p in EC is not yet clears [16]. Studies have found that miR-199a/b-5p may target and regulate the EMT signalling pathway through FAM83B, inhibiting

the invasion and metastasis of EC [17]. MiR-501 can regulate the expression of HOXD10, thereby affecting the proliferation and invasion ability of EC [18].

This study comprehensively analyses the comprehensive research of miR-421 in EC diagnosis based on previous literature research, to clarify the application and mechanism of miR-421 in EC diagnosis. We found that the comprehensive sensitivity (95% CI: 0.71-0.84) and specificity (95% CI: 0.79-0.86) of miR-421 for EC showed high clinical application value in the diagnosis of EC. According to the Spearman correlation test, there was no significant threshold effect between the experiments [19]. Subgroup analysis demonstrated that there may be differences in the patient's place of birth, with a comprehensive sensitivity of 0.80 (95% CI: 0.71~0.86); The specificity is 0.77 (95% CI: 0.63~0.87), the I^2 value is 0, and p=12%.

Based on previous literature research, this study comprehensively analysed the role of miR-548ag in EC diagnosis, to clarify the application and mechanism of miR-548ag in EC diagnosis. The sensitivity and specificity of the 7 selected articles in this study were 0.79 and 0.89, respectively. The Spearman test results indicated that there was no dramatic threshold effect among the patients participating in the experiment. The sensitivity, specificity, and SROC curve product of miR-548ag for EC all showed that miR-548ag has high clinical application value in EC. In addition, when analysing subgroups, like the miR-421 group, the differences in patients in China were significantly reduced. The above research indicates that miR-548ag has high diagnostic value for EC and can be used for precise diagnosis of EC.

In the prognostic analysis of miR-421, this project included 10 articles. MA revealed that miR-421 was associated with the prognosis of EC, with HR of 1.40 (95% CI: 1.01-1.94) and I^2 of 75.70%. These results indicate that miR-421 expression is elevated in EC and is closely related to the prognosis of EC. Due to the high heterogeneity of this study, we used a random influence model for analysis. Subgroup analysis was conducted on patient source, EC type, and sample type. The results showed that among these factors, patient source, EC type, and sample type may be the main reasons for heterogeneity. To investigate the stability of the conclusions obtained in this study, sensitivity analysis was performed by excluding one group of studies at a time and recalculating the merged HR at the same time. The outcomes indicated that miR-421 was highly expressed in EC and closely correlated with the prognosis of EC.

In the prognostic analysis of miR-548ag, our research group collected a total of 8 cases. The relevant outcomes revealed that the HR was 1.62 (95% CI: 1.30-2.01), and I^2=65.90%. Based on this, a random effects model was established. Research has found that overexpression of miR-548ag is relevant to the prognosis of EC patients. The outcomes revealed that compared with the miR-421 group, only a significant decrease in sample size was observed, indicating that EC type, sample type, etc. are not the main reasons for EC heterogeneity, but rather the source of patients. Sensitivity analysis was conducted on the overall survival rate of OS, and no significant impact was found on the combined HR and 95% CI in any study, indicating the reliability of this analysis.

Finally, for investigating the publication bias of our meta-analysis, the Deeks' funnel plot was utilized for evaluating diagnostic analysis, and the funnel plot, Begg's test, and Egg's test were utilized for evaluating the publication bias of prognostic analysis [20]. Only in the diagnostic study of miR-421 for EC, the Deeks' funnel plot indicates that there may be publication bias between studies (p=0.04). Other subsequent analyses have further demonstrated the role of miR-421 and miR-548ag in EC. However, there are still some shortcomings in the meta-analysis of this study: (1) the research on ethnic factors is not sufficient, and the statistical data is single. For example, diagnostic meta-analysis targets populations in Asia and Europe, while predictive meta-analysis targets populations in the Americas and Asia. Therefore, in future research, more attention should be paid to the impact of ethnicity on EC. (2) Due to the small sample size, only 6 cases of miR-421 and 7 cases of miR-548ag have been diagnosed and analysed, while only 10 cases of miR-421 and 8 cases of miR-548ag have been predicted and analysed in predictive analysis. These data will affect the credibility of the results of this study. This project aims to further expand the sample size and clarify the functions of miR-421 and miR-548ag in EC progression. (3) This study only focuses on the diagnostic and prognostic value of miR-421 and miR-548ag in EC, without discussing the value of their combination.

Therefore, we speculate that miR-421 and miR-548ag may become early diagnostic and prognostic molecular markers for EC, with high expression significantly lower than low expression patients. As far as the development of tumour is concerned, a single biomarker cannot determine the development process of tumour. On this basis, combining multiple molecular markers will help elucidate the internal mechanisms of tumour OAD, and reveal the external factors of tumour OAD. This project aims to combine miR-421/miR-548ag with conventional molecular markers to achieve accurate diagnosis of EC. This study will elucidate the molecular mechanisms of miR-421 and miR-548ag in the OAD of EC, laying a theoretical foundation for early diagnosis of EC. This project aims to further investigate the role of miR-421 and miR-548ag in the OAD of EC based on research in the past, and combine them with other miRNAs for further studying the role of miR-421 and miR-548ag in the OAD of EC, providing new ideas for the prevention and control of EC.

Conclusion:

This study explored the relation in immune related biomarkers and prognosis of endometrial cancer through meta-analysis. The research results indicate that miR-421 and miR-548ag may be biomarkers for the prognosis of endometrial cancer, and these findings have important guiding significance for in-depth understanding of the pathogenesis, pathological and physiological changes, and clinical treatment of endometrial cancer. However, this study also has some limitations, such as limited literature inclusion and insufficient data sources. Therefore, it is essential to carry more research in the future for verifying the influence of these biomarkers in the prognosis of endometrial cancer, as well as to explore other possible biomarkers, for gaining a more comprehensive understanding of the pathogenesis and pathophysiological changes of endometrial cancer and provide more effective reference for clinical treatment.

References

1. Vliet H , Aa M , Siebers A G , et al. Endometrial cancer prognosis in women with endometriosis and adenomyosis: A retrospective nationwide cohort study of 40 840 women[J]. International Journal of Cancer, 2022, 150(9):1439-1446.
2. Bernard L , Kwon J S , Simpson A N , et al. The Levonorgestrel Intrauterine System for Prevention of Endometrial Cancer in Women With Obesity: A Cost-effectiveness Study[J]. OBSTETRICAL & GYNECOLOGICAL SURVEY, 2021, 76(10):605-606.
3. Jamieson A , Huvila J , Thompson E F , et al. Variation in practice in endometrial cancer and potential for improved care and equity through molecular classification[J]. Gynecologic oncology, 2022, 165(2):201-214.
4. Atakul, Tolga, Altinkaya, S. Ozlem,Abas, Burcin Irem,Yenisey, Cigdem.Serum Copper and Zinc
5. Levels in Patients with Endometrial Cancer[J].Biological trace element research.,2020, 195(1):46-54. [5]Siegenthaler F , Lindemann K , Epstein E , et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification[J]. Gynecologic oncology, 2022, 165(2):230-238.
6. Inoue F , Sone K , Toyohara Y , et al. Histone arginine methyltransferase CARM1 selective inhibitor TP-064 induces apoptosis in endometrial cancer[J]. Biochemical and Biophysical Research Communications, 2022, 601:123-128.
7. Post C C B , Westermann A M , Boere I A , et al. Efficacy and safety of durvalumab with olaparib in metastatic or recurrent endometrial cancer (phase II DOMEC trial)[J]. Gynecologic oncology, 2022, 165(2):223-229.
8. Akildzhonov F R , Buziashvili J I , Stilidi I S , et al. Biomarkers in patients after chemotherapy[J]. Medical Alphabet, 2021(19):49-53.
9. Hu X , Dai Z , Pan R , et al. Long-term transplantation human menstrual blood mesenchymal stem cell loaded collagen scaffolds repair endometrium histological injury[J]. Reproductive Toxicology, 2022, 109:53-60.

10. Mielikhova T V , Gryshchenko O V , Lazurenko V V , et al. Optimization of diagnostic studies in patients with adenomiosis and/or hyperplastic processes of endometrium[J]. Reproductive Endocrinology, 2021(58):34-39.
11. Kazantseva E V , Tral T G , Tolibova G K . Clinical and anamnestic data and morphofunctional characteristics of the endometrium in women with uterine developmental anomalies[J]. Journal of Obstetrics and Women S Diseases, 2021, 70(2):5-12.
12. J Rubio-Pérez,R Hernández,T Hernández,B Doger,V Casado,V Moreno.Dostarlimab for the treatment of endometrium cancer and other solid tumors.[J].Drugs of today.,2021,57(3):187-197. [13] Jackson C C , Cantrell L , Erickson B K , et al. A phase II trial of bevacizumab and rucaparib in recurrent carcinoma of the cervix or endometrium[J]. Journal of Clinical Oncology, 2021, 39(15_suppl):5527-5527.
13. Deshmukh B D , Malpani A , Gosavi A V , et al. HISTOPATHOLOGICAL STUDY OF
14. ENDOMETRIUM IN WOMEN WITH ABNORMAL UTERINE BLEEDING[J]. International
15. Journal of Scientific Research, 2021:30-33.
16. Weelden W , Reijnen C , Bronsert P , et al. The cut-off for estrogen and progesterone receptor in endometrial cancer revisited: an ENITEC collaboration study[J]. Human Pathology, 2021, 109:80-91.
17. Zmen S , Kurt S , Ilgen O , et al. Comparison of MRI, CA-125 and HE-4 in determining the depth of myometrial invasion in cases with endometrial cancer[J]. Journal of Clinical and Investigative Surgery, 2021, 6(1):22-29.
18. Cintesun, Feyza Nur Incesu,Kerimoglu, Ozlem Secilmis,Cintesun, Ersin,Nergiz, Suleyman,Acar, Hasan,Celik, Cetin.The relationship between KRAS LCS6 polymorphism and endometrium cancer[J].Journal of obstetrics and gynaecology: the journal of the Institute of Obstetrics and Gynaecology,2020,40(7):988-993.
19. Arslan, Ayse Kubra Karaboga,Pasayeva, Leyla,Esen, Merve Ayse,Tugay, Osman.Synergistic Growth Inhibitory Effects of Eryngium kotschyi Extracts with Conventional Cytotoxic Agents: Cisplatin and Doxorubicin against Human Endometrium Cancer Cells[J].Current pharmaceutical biotechnology,2022,23(5):740-748.
20. Reid H , MKMD Oca, Fayanju O M , et al. 92741 Racial differences in patient-reported distress among women with endometrial cancer[J]. Journal of Clinical and Translational, Science 2021, 5(s1):86-87.
21. Editorial A . Proceedings of the Expert Council "Treatment of inoperable endometrial cancer in Russia: issues that have not yet been addressed"[J]. Tumors of Female Reproductive System, 2021, 17(1):65-69.