RESEARCH ARTICLE

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Alterations of Inflammatory Mediators (*TNF-α* and *HMGB1*) and Circulating *microRNA-22* Expression in Pre- and Post-Menopausal Women with Early-Stage Epithelial Ovarian Cancer

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Abstract

Background: Ovarian cancer is an important cause of cancer-related mortality among women, disease severity increases due to hormonal changes, which modify the ovarian environment and may contribute to the development of ovarian cancer (OC). Inflammatory mediators play a central role in the enhancement of OC progression. Several microRNA play central role in OC; *microRNA-22* (*miR-22*) is a biomarker associated with hormonal status regarding menopause and the development of ovarian cancer. Evaluating these biomarkers and assess the interaction among them, may contribute to a deeper understanding of the disease mechanism and can improve diagnostic accuracy. **Objective:** Assess *CA125*, *TNF-α*, *HMGB1*, and *miR-22* levels in pre- and post-menopausal epithelial ovarian cancer (EOC) patients as well as the correlation of these factors and their impact on EOC progression in pre- and post- menopausal patients. **Methods:** 120 women enrolled in this study were divided into four groups (n=30 for each group): two control groups (healthy premenopausal and postmenopausal) and two patient groups (premenopausal and postmenopausal with EOC). Serum levels of *CA125*, *TNF-α*, *HMGB*, and *miR-22* expression were measured. Statistical analysis was performed to compare groups and to assess correlations within patient groups at ($p< 0.05$) using SPSS Statistics analysis version 26. **Results:** All biomarkers showed statistically significant differences among groups at $p < 0.05$. levels of *CA125*, *HMGB1*, and *TNF-α* were significantly increased in EOC groups Especially in the postmenopausal group. Expression of serum *miR-22* was significantly decreased in EOC patient groups compared to control groups. Regarding correlation analyses, there were positive associations between *TNF-α* and *HMGB1* in patient groups. Conversely, the expression of miRN-22 was inversely correlated with *HMGB1*. **Conclusions:** The relative expression level of *miR-22* significantly decreases depending on menopausal and inflammatory status, suggesting that *miR-22* plays as tumor suppressor role and is negatively affected by inflammation.

Keywords: Ovarian cancer, Menopause, Post menopause, *miR-22*, Inflammatory Cytokines, *HMGB1*, *TNF-α*

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Introduction

Ovarian cancer (OC) is one of the most fatal malignancies and is characterized as a major health challenge for women worldwide that increasing burden [1]. It considers the fifth grades of the leading mortality among women suffering cancer [2]. The incidence of OC differs globally, several factors can be influenced like geographical, genetic, and lifestyle. The highest percentage of incident of OC in Asia (54%) as documented by GLOBOCAN (2023). There are several subtypes of ovarian cancer "epithelial tumors, germ cell tumors, sex cord-stromal tumors, and metastatic lesions". Epithelial ovarian cancer (EOC) is considered the most common type among these types, where it reaches more than 95% while other type nearly 5% [3]. Advanced age-related menopause, a family history of ovarian or breast cancer, and hereditary mutations in tumor suppressor genes, particularly BRCA1 and BRCA2 all these factors increase the risk of EOC occurrence [4].

Despite advances in techniques involving surgical, and chemotherapeutic for therapy, but the prognosis for OC remains poor because of late diagnosis. The most test widely used for diagnosis EOC is serum cancer antigen 125 (CA-125) "a glycoprotein encoded by the MUC16 gene". Although CA-125 is usually utilized to monitor the

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progression and severity of disease as well as response to treatment, its diagnostic utility as an independent biomarker still suboptimal [5].

Inflammation has been linked with EOC; Chronic inflammation of the ovarian surface epithelium has been related in severity of disease. Pro-inflammatory cytokines play a pivotal role as key mediators in the pathogenesis of EOC. The important cytokine is tumor necrosis factor-alpha (*TNF-α*) that playing central roles in enhancing and development of tumor [6, 7], it is secreted by several innate and adaptive immune cells, and contributes to various oncogenic processes like angiogenesis, apoptosis resistance, cellular proliferation, and immunological evasion that led to progression and severity of disease. Although *TNF-α* usually considers a mediator of anti-tumor immunity, *TNF-α* may has contrary role by induces tumor progression because of the tumor microenvironment effects [8].

Another cytokine is High Mobility Group Box 1 (*HMGB1*), "a nuclear protein" has two functions in cancer biology. *HMGB1* can be either actively secreted or passively released from damaged necrotic cells as a pro-inflammatory mediator. In Intracellular, function of *HMGB1* is related in Preservation and repairing of DNA, while in extracellular it stimulates immunity and inflammatory responses that stimulate tumor growth [9, 10]. high levels of *HMGB1* have been detected in most type of cancer including OC, therefor its utility as a potential prognostic indicator [11].

microRNAs (miRNAs) are small (20–28 nucleotides) non-coding RNAs that regulate gene expression post-transcriptionally. Circulating miRNAs is a novel biomarker for the early detection of various types of disease including cancer, predict the disease progression and severity. The stability of miRNAs in biological fluids such as blood, urine, and serum make them as an important indicator [12, 13]. miRNAs have different function in cancer some of these as oncogenes and other as tumor suppressors, that play complex roles in tumorigenesis [14].

Among the miRNAs associated with ovarian cancer, an in vitro study about OC have shown that *microRNA-22* (*miR-22*) has potential role as tumor suppressor through its role in inhibited cell migration and infiltration [15]. Since menopause typically occurs around age 50 and involves hormonal changes like progesterone and estrogen, it is likely affecting the expression of miRNAs, including *miR-22*. However, there is currently no direct evidence to support this association.

It is well established that inflammatory mediators and miRNA expression play a significant role in malignancy; however, the specific interaction between them during the pre- and post-menopausal transition remains insufficiently understood. Therefore, this study aimed to evaluate *miR-22* expression levels and their simultaneous association with *TNF-α* and *HMGB1* in pre- and post-menopausal women with early-stage epithelial ovarian cancer. The goal was to assess their potential as complementary biomarkers that could provide more accurate diagnostic insights across different reproductive stages, which significantly influence the systemic inflammatory environment and gene expression profiles, potentially accelerating tumor progression. This study could fill an important gap by providing more accurate diagnostic perspectives on the disease.

Materials and Methods

This study was performed at Al-Diwaniyah Teaching Hospital / Department of oncology, and at University of AL-Qadisiyah/ College of Science/Advanced Research Laboratory during the period between October 2024 to June 2025.

The total number are 120 women were participating in the study, categorized into four groups (n=30 for each group): groups as control are Healthy premenopausal women, and Healthy postmenopausal women, other groups are Premenopausal women and Postmenopausal women with early-stage EOC.

Patients were newly diagnosed with the serous histological subtype of EOC based on clinical presentation, pelvic ultrasound findings, and elevated serum *CA-125* levels. The diagnosis was confirmed by histopathology, and staging was established according to the International Federation of Gynecology and Obstetrics (FIGO) criteria (Stage I or II). blood samples were collected at the time of initial clinical diagnosis, prior to any biopsy, received chemotherapy, radiotherapy, or surgical intervention.

All patients were newly diagnosed with the serous histological subtype of EOC. To ensure the integrity of molecular and inflammatory markers, blood samples were collected at the time of initial clinical diagnosis, prior to any biopsy, surgical intervention, chemotherapy, or radiotherapy.

Inclusion criteria

Women aged ≥25 years with newly diagnosed histologically confirmed EOC, who had not received any prior treatment. Written well-informed agreement was obtained from all participants.

Exclusion criteria

Women with any other histological types of ovarian tumors, advanced-stage OC, prior or after treatment with chemotherapy, radiotherapy, or surgery, coexisting malignancies or chronic inflammatory conditions, and chronic diseases such as diabetes, hypertension, or immune disorders were excluded from the stud

Sample Analysis

Blood sample allowed to clot for 20-30 minute after withdrawing from venous of subjects, the serum was extracted by centrifugation at 3600 rpm for 10-15 minutes at 4 °C, and divided into four parts: one stored at -80°C for *miR-22* analysis. The expression of *miR-22* was measured using quantitative polymerase chain reaction (qPCR). RNA was extracted from 0.3 mL of serum using TRIzole™ reagent, and cDNA was generated using the Proto-script® first-strand cDNA synthesis kit (NEB, UK). The Polymerase Chain Reaction was performed using Luna Universal qPCR Master Mix (NEB, UK). The complementary DNA produced was mixed with forward and reverse universal primers for *miR-22* and the

cDNA Bright Green master mix. As an internal control, gene U6 was used (Table 1). The proportional showed an expression fold change of *miR-22* ($2^{-\Delta\Delta Ct}$), were calculated by threshold cycle (Ct). and the other parts are stored at -20°C. *CA125* levels, *HMGB*-1level, and *TNF-α* were measured by "Enzyme-Linked Immunosorbent Assay (ELISA)" ELISA Kit, Elabscience, China. All serum samples and molecular assays were analyzed in duplicate to ensure analytical reliability. Any samples showing significant variability were retested to confirm the accuracy of the results.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 26. One-way Analysis of Variance (ANOVA) was performed to compare the mean levels of biomarkers across the study groups. Post-hoc comparisons were conducted using Tukey's HSD test to determine specific group differences. Correlation analyses were conducted using Pearson's correlation coefficient. A p-value < 0.05 was considered statistically significant.

Results

Table 2 summarizes the demographic characteristics of the study participants. A total of 120 individuals were included: 60 ovarian cancer patients (30 premenopausal, 30 postmenopausal) and 60 healthy controls (30 premenopausal, 30 postmenopausal). As expected, age differed significantly between pre- and postmenopausal groups (P < 0.05), confirming appropriate stratification by menopausal status, but no significant differences were observed between healthy and cancer groups within the same menopausal category. Mean BMI did not significantly differ among healthy groups (25.5 ± 3.5 vs. 26.18 ± 1.61 kg/m²) or between healthy and premenopausal cancer patients (26 ± 0.16 kg/m²). However, postmenopausal cancer patients showed significantly lower BMI (23 ± 3.62 kg/m², P < 0.05), suggesting a potential impact of disease status on BMI after menopause.

Table 3 and Figure 1 shows the comparison of *CA125*, *HMGB1*, *TNF-α*, and *miR-22* among study groups. No significant differences were observed between healthy premenopausal and postmenopausal women for *CA125* (P = 0.9658), *HMGB1* (P = 0.8716), or *TNF-α* (P = 0.3123) respectively. However, all three markers were significantly raised in EOC patients compared with control groups (P < 0.05), postmenopausal cancer patients showing the highest levels. The relative gene expression of *miR-22* showed a progressive decrease across the studied groups. The highest expression was observed in healthy premenopausal

Table 1. Primers Used for Quantifying Mature miR-22

Primers	Sequence (5′→3′)	length	Amplicon Size (bp)
miR-22_RT	GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACTAAAGC	47	_____
miR-22For	GAGCTGCACTGACCAGTAGG	20	99
miR-22Rev	GTGCTGGCAGATGGATCACT	20	
U6 For	GAGAAGATTAGCATGGCCCCT	21	60
U6 Rev	ATATGGAACGCTTCACGAATTTGC	24	

Table 2. Demographic Characteristics of the Study Participants

Variable	Healthy Pre-M	Healthy Post-M	EOC Pre-M	EOC Post-M	P value
Age (year)	32.42±3.47A	55±3.28B	31.49±4.6A	57.63±3.63B	< 0.05
BMI (Kg/m²)	25.5±2.5A	26.18±1.61A	26±0.16A	23±2.62B	< 0.05

Pre-M (premenopausal), post-M(postmenopausal). The same coordinating letters are not significantly different, whereas different coordinating letters differ significantly (P < 0.05).

Table 3. Summarizes the Comparison of Biomarkers (*CA125, HMGB1, TNF-α* and *miR-22*) between the Four Groups

Characteristic	Healthy Pre-M	Healthy Post-M	EOC Pre-M	EOC Post-M	P value
CA125 (U/ml)					
Mean ± STD	19.53 ± 4.11^{A}	16.00 ± 3.62^{A}	162.7 ± 25.78^{B}	204.4 ± 45.11^{C}	< 0.05
HMGB1 (ng/ml)					
Mean ± STD	5.00 ± 2.1^{A}	5.99 ± 1.73^{A}	22.58 ± 7.8^{B}	28.93 ± 5.59^{C}	< 0.05
TNF-α (pg/ml)					
Mean ± STD	13.90 ± 2.01^{A}	15.01 ± 1.44^{A}	19.97 ± 1.97^{B}	23.03 ± 3.84^{C}	< 0.05
miR-22 Relative Gene Expression					
Mean ± STD	1±0^{A}	0.82±0.05^{B}	0.63±0.08^{C}	0.43±0.08^{D}	< 0.05

Pre-M (premenopausal), post-M(postmenopausal). The same coordinating letters are not significantly different, whereas different coordinating letters differ significantly (P < 0.05)

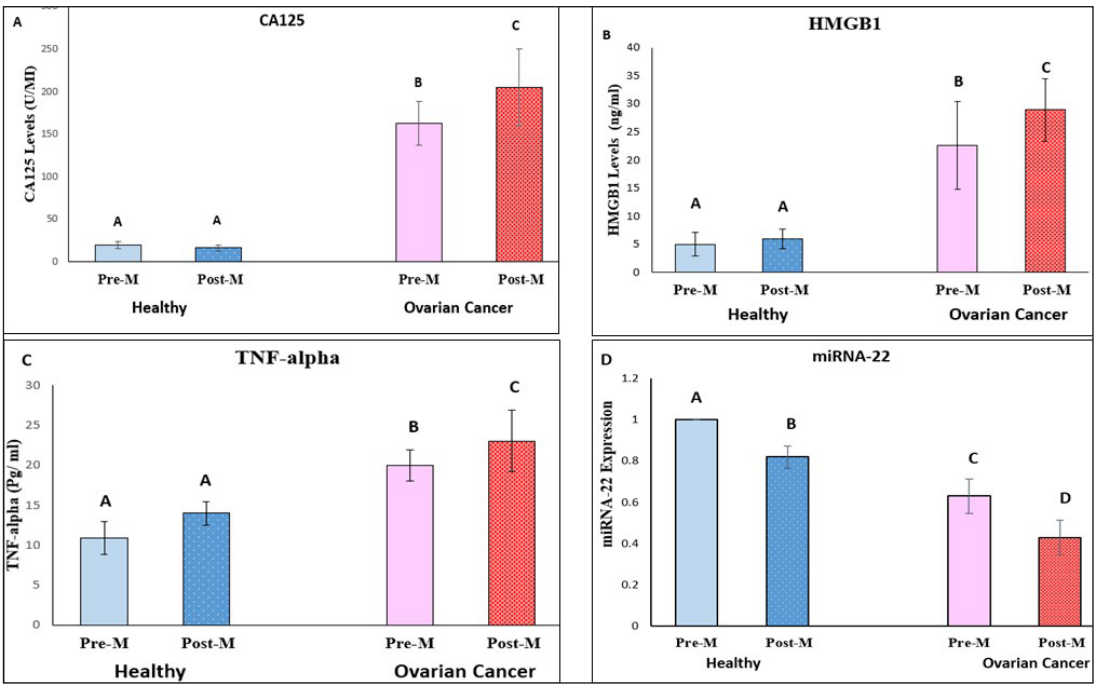

Figure 1. Comparative Analysis of *C125* (A), *HMGB1*(B), *TNF-alpha* (C), and *miR-22* (D) levels in Pre- and Postmenopausal women with and without Ovarian Cancer.

women (1 ± 0), followed by healthy postmenopausal women (0.82±0.05), premenopausal patients with EOC (0.63 ± 0.08), and the lowest expression was detected in postmenopausal patients with EOC (0.43 ±0.08). The differences among groups were statistically significant ($p < 0.05$).

The correlation analysis in Table 4 shows the relationship between the studied biomarkers in premenopausal EOC patients. A moderate to strong positive association was observed between TNF-α and *HMGB1* (r = 0.699, p = 0.005). Conversely, *HMGB1* demonstrated a moderate significant inverse correlation with circulating *miR-22* levels (r = –0.502, p = 0.004). In postmenopausal EOC patients (Table 5), correlation analysis detected a strong positive correlation between

Table 4. Correlation between Serum *TNF-α, HMGB1, CA125*, and *miRNA* Expression Levels in Premenopausal Epithelial Ovarian Cancer Patients

Characteristic	Correlation	*HMGB1*	*CA125*	*miRNA-22* Level
TNF-α	Pearson r	0.699	0.06	-0.204
	P value	0.005	0.751	0.28
HMGB1	Pearson r	1	0.271	-0.502
	P value		0.15	0.004
CA125	Pearson r		1	-0.05873
	P value			0.497

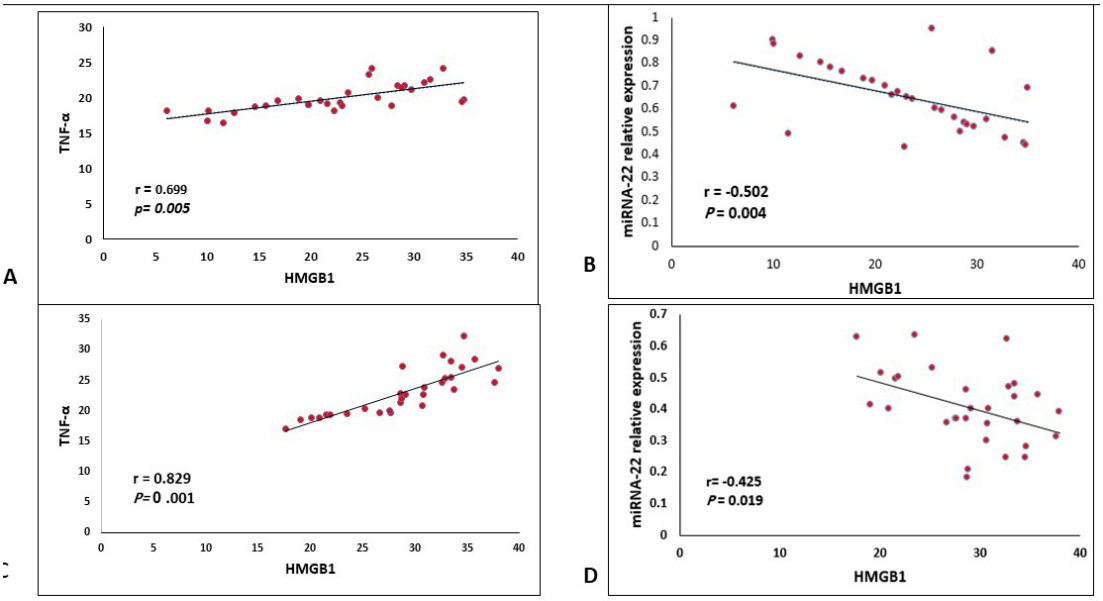

Figure 2. Correlation between Serum *HMGB1, TNF- α* and *miR-22* Expression in Premenopausal (A, B) and postmenopausal (C, D) women with ovarian cancer.

Table 5. Correlation between Serum *TNF-α, HMGB1*, *CA125*, and *miRNA* Expression Levels in Postmenopausal Ovarian Cancer Patients

Characteristic	Correlation	*HMGB1*	*CA125*	*miRNA-22* Level
TNF-α	Pearson r	0.829	0.183	-0.234
	P value	0.001	0.334	0.213
HMGB1	Pearson r	1	0.294	-0.425
	P value		0.668	0.019
CA125	Pearson r		1	-0.15549
	P value			0.183

TNF-α and *HMGB1* (r = 0.829, p = 0.005). In contrast, *HMGB1* showed a moderate significant inverse correlation with circulating *miR-22* levels (r = −0.425, p = 0.019).

Discussion

As expected, age differed significantly between premenopausal and postmenopausal groups (P < 0.05). The observed BMI reflects menopausal and cancer-related metabolic changes.

In healthy women, BMI remains relatively stable with age. However, elevated BMI in premenopausal women is linked to increased ovarian cancer risk [16] due to obesity-related hormonal and inflammatory changes [17].

Conversely, postmenopausal cancer patients showed significantly lower BMI, likely due to early cancer-induced metabolic dysregulation rather than protective effects of lower weight [18].

In the present study, *CA125* levels were higher, though not statistically significant, in healthy premenopausal women compared to postmenopausal controls. This pattern is consistent with previous reports suggesting that hormonal activity, endometrial shedding, and cyclical ovarian function are associated with elevated baseline CA-125 levels in pre-menopausal women. These levels typically decrease after menopause [19], which may be attributed to the cessation of these physiological processes

In EOC patients, this difference is unlikely to reflect more advanced disease, as all cases were at similar stages; instead, it is potentially linked to post-menopausal physiological changes rather than disease progression. Several factors may collectively contribute to this, such as reduced clearance of circulating glycoproteins, alterations in peritoneal fluid dynamics, and hormonal modulation of tumor marker expression, which together can enhance the detectability of tumor-derived CA-125 in older women [20, 21].

High level of inflammatory mediators *HMGB1* reflects the active secretion from malignant cells and immune cells, that binding to receptors such as RAGE and TLRs, therefor leading to increase inflammatory signaling and tumor progression [22]. Increased *HMGB1* levels in postmenopausal patients may be related to alterations of immune clearance mechanisms or modification *HMGB1* receptor expression that linked with aging and disease progression [23]. Results proved *HMGB1* levels unchanged in healthy control groups but increase markedly in EOC patients, supporting its role as a biomarker related with EOC even in early stage.

The levels of pro-inflammatory *TNF-α* were increase significantly in both patient groups. This result reflects the role of *TNF-α* as a pivotal cytokine involved in inflammatory responses linked with EOC [21]. The insignificant increase in *TNF-α* levels was observed in healthy postmenopausal women linked with the state of low-grade inflammation associated with aging [24].

In EOC patients, the elevated biomarkers *TNF-α*, *CA125* and *HMGB1* levels suggesting there is an interconnected relationship between inflammation stimulation and immune response activation with EOC. Both *HMGB1* and *TNF-α* stimulate inflammation in tumor microenvironment that enhanced tumor progression and immune evasion through activation of NF-κB pathway that induced cytokine secretion and tumor promotion [25]. Elevated *CA125* may affected by inflammatory environment within the tumor milieu [5].

Circulating microRNAs contribute in many pathogenic pathways [13, 26]. The study observed decrease in the level of *miR-22* expression in patient groups. *miR-22* expression possibly reflects the pathological dysregulation, downregulated of *miR-22* in malignancies of women like OC, revealing that *miR-22* has a key role as tumor-suppressive [27]. These findings align with previous studies reporting decreased *miR-22* expression in cancers and suggest that *miR-22* could serve as both a biomarker of disease severity and a possible therapeutic target [28].

The significant reduction of *miR-22* in healthy postmenopausal women compared to healthy premenopausal women may attributed to hormonal changes associated with menopaus, study showed there are several circulatory miRNAs upregulated or downregulated depend on estrogen level in serum [29].

About correlation in Table 4, and 5 for patient groups, there is different interactions among the studied biomarkers of EOC patients. A strong positive correlation between TNF α and *HMGB1* that supports these cytokines as mediators to increase inflammation that led to enhancement the tumor environment. *HMGB1* released from damaged cells and promotes cytokine release through TLR4- and NF κB-dependent pathways, which in turn drive TNF α production that implicated in inflammatory responses and cancer progression [30].

Conversely, *HMGB1* showed a significant negative correlation with *miR-22* levels in the patient groups. Previous studies have revealed that *miR-22* can reduce inflammation by contributing to the suppression of *HMGB1* via the *HMGB1*-TLR4-NF-kB pathway [31]. Increased expression of *HMGB1* in EOC is associated with poor prognosis and reduced survival [32]. *CA125* showed no significant relationship with *TNF-α*, *HMGB1*, or *miR-22* levels, suggesting that *CA125* remains a suitable marker for predicting EOC progression [33]. The interaction of *HMGB1* and *TNF-α* with miRNAs may represent a key regulatory mechanism in EOC progression.

Study limitation

This study has some limitations that must be acknowledged, despite its important findings. These

include the relatively small sample size, which may limit the generalizability of the results. Furthermore, it was conducted only at a single center within a specific region. Therefore, further longitudinal studies across multiple centers and regions with larger cohorts are recommended to verify the clinical utility of these biomarkers across a diverse population.

In conclusions, downregulation of *miR-22* can play as anti-inflammatory role in ovarian cancer, reduction of *miR-22* combining with increased inflammatory markers like *TNF-α* and *HMGB1* levels in patient groups especially menopausal women patients, that may enhance menopause-related diagnostic mechanism depend on the interaction between these markers, and could consider novel therapeutic goals for modulating inflammatory pathway in EOC. Further studies about EOC should take into consideration the menopausal state when interpreting inflammation condition. Larger groups are recommended to improve the predictive results and investigate the integration of these parameters in clinical screening, in order to understand ovarian cancer diagnostic strategies.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

Ethical approval

The study protocol, including all procedures related to blood sample collection, and laboratory analyses was approved by the Ethics Committee of the University of Al-Qadisiyah (QU-IRB-2024-097), and complied with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment and sample collection.

Data Availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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