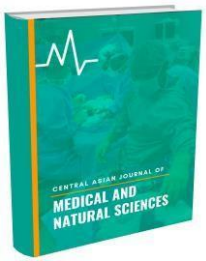

CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
https://cajmns.centralasianstudies.org/index.php/CAJMNS
Volume: 06 Issue: 04 | October 2025 ISSN: 2660-4159

Article

Shedding Light on Ovarian Cancer: MicroRNA-590 and FOXA2 as Novel Diagnostic Signatures

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Abstract: In recent years, there has been a lot of interest in the study for particular biomarkers in ovarian cancer. By targeting tumor suppressors, microRNA-590 has been shown to increase the proliferation of ovarian cancer cells and plays a significant role in the formation of tumors. Numerous cancers, including ovarian cancer, have decreased expression of the tumor suppressor transcription factor FOXA2. The purpose of this study was to assess the diagnostic value of circulating MicroRNA-590 and FOXA2 levels in patients with ovarian cancer. A case-control study comprising 35 healthy controls and 70 ovarian cancer patients was carried out. ELISA was used to measure the levels of FOXA2 in the serum. Using qRT-PCR, the amount of circulating MicroRNA-590 was measured. The 2^-ΔΔCt technique was used to calculate fold change values. ROC curve and logistic regression were used in statistical analysis to compare groups and assess diagnostic value. Compared to controls, ovarian cancer patients had significantly reduced levels of FOXA2 and MicroRNA-590 expression. MicroRNA-590 fold change values were found to have significantly decreased. MicroRNA-590 had an efficient diagnostic value (AUC = 84.5%), according to ROC curve analysis, whereas FOXA2 had limited diagnostic performance. Both indicators' diagnostic significance was validated using logistic regression. MicroRNA-590 and circulating FOXA2 levels are decreased in ovarian cancer and could be useful non-invasive diagnostic indicators. Superior diagnostic accuracy was demonstrated by MicroRNA-590, which may help in early diagnosis and differentiation from healthy individuals.

Keywords: MicroRNA-590, FOXA2, Ovarian Cancer, Fold Change

Citation: Saddam, Z. A., Hameed, R. M., & Omran, Z. S. Shedding Light on Ovarian Cancer: MicroRNA-590 and FOXA2 as Novel Diagnostic Signatures. Central Asian Journal of Medical and Natural Science 2025, 6(4) 1851-1862.

Received: 30th Jun 2025
Revised: 07th Jul 2025
Accepted: 29th Jul 2025
Published: 15th Aug 2025

1. Introduction

With their unique aetiology, origin, pathophysiology, differentiation, patterns of spread, and molecular profiles, ovarian tumors are an extensive group of malignant disorders [1]. The 2020 World Health Organization (WHO) categorization of OC includes sex cord–stromal tumors (2–5%), germ cell tumors (5%), and epithelial (EOC; 90%). EOCs (i.e., ovarian carcinomas) are the most common OC type, encompassing five main subtypes that are distinguished based on molecular analysis, histologic and immune profile: high-grade serous (HGSC; 70%), endometrioid (EC; 10%), clear cell (CCC; 10%), low-grade serous (LGSC; 5%) and mucinous (MC; 3%) carcinomas [2] . The diagnostic complexity of ovarian cancer continues to challenge clinicians due to the disease's silent clinical course and the absence of highly sensitive blood-based screening tools [3-4]. Although common markers like HE4 and CA-125 are employed in clinical settings, their shortcomings in early-stage identification and specificity highlight the need for new biomarkers [5-6]. As

molecular oncology advances, circulating non-coding RNAs and transcription factors have emerged as promising candidates to improve diagnostic precision.MicroRNA-590 (miR-590) is a small non-coding RNA located on chromosome 7q11.23 that regulates post-transcriptional gene expression and is implicated in various oncogenic pathways [7-8]. Its altered expression has been reported in several malignancies including cervical, breast, and liver cancers [9]. By targeting tumor suppressors such cyclin G2, miR-590 seems to act as an oncogenic miRNA in the context of ovarian cancer, promoting cell survival and proliferation [10]. Therefore, measuring the fold change of circulating miR-590 could offer a non-invasive way to detect the presence of disease [11-12]. Forkhead Box A2 (FOXA2) FOXA2, a member of the forkhead box family of transcription factors, has been shown to regulate gene expression linked to metabolic homeostasis and cellular differentiation [13]. Numerous solid tumors, particularly ovarian cancer, have been shown to exhibit decreased FOXA2 expression; this downregulation has been linked to worse outcomes and increased invasiveness [14-15]. Of particular importance is the interaction between FOXA2 and miR-590. According to evidence, miR-590 may directly target FOXA2, lowering its expression and encouraging the growth of tumors [16].

This study aims to investigate the diagnostic significance of circulating miR-590 and FOXA2 in women with ovarian cancer.

2. Materials and Methods

Study Design

A case-control research using 105 samples—70 sick samples and 35 healthy control samples—was part of the current effort. From January 2024 to August 2025, ovarian cancer patients were gathered from Imam Al-Hussein Medical City's oncology unit and Imam Al-Hassan Al-Mujtaba Hospital in Kerbala.

Sample Collection

Via venipuncture, five milliliters of blood were extracted. For fifteen minutes, four milliliters of blood were allowed to stand at room temperature in a gel tube. Centrifugation was used for 10 minutes at about 4000 xg to separate the serum. The samples were stored at −80°C

Exclusion and Inclusion criteria

Women with histopathologically confirmed ovarian cancer diagnoses met the patient group's inclusion requirement. Any prior history of other cancers was one of the exclusion criteria.

Thirty participants (35 women) in the control group appeared to be in good health and had no prior history of cancer. The patient group's age and gender distribution was matched, and a self-reported questionnaire was used to gather demographic information.

Measurement of FOXA2 and miR-590 Expression

FOXA2 concentration was measured using a Sandwich-ELISA kit (E7843Hu, BT LAB, China), Standard Curve Range: 0.19-12ng/ml. based on a pre-coated antibody, biotinylated antibody, Streptavidin-HRP, substrate solution, and absorbance reading at 450 nm.

Total RNA was extracted from blood samples using Total RNA Mini Kit (Genaid, Taiwan). qRT-PCR was performed with TransScript® Green One-Step SuperMix (TransGen Biotech, China), using primers specific for miR-590 and U6 (Macrogen, Korea). Relative expression levels of miR-590 were calculated using the 2-ΔΔCt method, where $\Delta Ct = Ct(miR\text{-}590) - Ct(U6)$ and $\Delta\Delta Ct = \Delta Ct(sample) - \Delta\Delta Ct(calibrator)$ [17].

Ethical Approval

Prior to their inclusion in the study, each patient and control patient provided valid verbal agreement and the hospital administration obtained valid written, signed consent.

Before the samples were taken, the technique was explained. The oncology unite in imam Al-Hussein Medical city & imam Al-Hassan Al-Mujtaba Hospital in Kerbala city and Kerbala Medical College's Ethical Committee both accepted the study's procedure (Research Ethics Committee Number (No. 24-62 dated October 9,2024))

Statistical Analysis

Real Statistics Resource Pack for Excel 2016 (Release 7.2) and SPSS version 28.0 (IBM, Chicago, IL, USA) were used for data analysis.. The Shapiro-Wilk test was used to determine normality, and descriptive statistics were employed. Non-conditional logistic regression was used to compute odds ratios with 95% CI. The best diagnostic thresholds were found using ROC curve analysis. A p-value of less than 0.05 was deemed significant.

3. Results

Table 1. Descriptive of the demographic characteristics of the study population (N=70).

Variable	Groups	N	%
Age. Groups	30-45 Years	16	22.9
	46-60 Years	37	52.9
	61-75 Years	17	24.2
BMI.groups	Normal weight	6	8.5
	Over weight	17	24.2
	Obesity	47	67.1
family history of disease	Yes	33	47.1
	No	37	52.8
educational level	Employees	5	7.1
	Housewife	62	88.5
	Retired	2	2.8
	Student	1	4.0
residence	Kerbala	40	57.1
	Babil	22	31.4
	Bagdad	3	4.2
	Naserha	2	2.8
	Diyala	3	4.2
Stage	Stage 1	10	14.2
	Stage 2	7	10
	Stage 3	11	15.7
	Stage 4	42	60
Grade	High	47	67.1
	Low	21	30
	Others	2	2.8
chemotherapy	Yes	62	88.5
	No	8	11.4
Metastasis	Yes	54	77.1
	No	16	22.8

Table 1 shows that most participants were aged 46–60 years (52.9%) and obese (67.1%). Positive family history was reported in 52.8%. The majority were housewives (88.5%) and resided in Kerbala (57.1%). Stage 4 was the most common (60%), and 67.2% had high-grade disease.

Table 2. Mean differences of biomarkers between Ovarian cancer patients & control groups.

Biomarker	Patients N=70	Control N=35	P value
FOXA2	3.09±1.98	3.72±3.03	0.025[S]
MicroRNA-590	19.21±11.86	5.25±2.95	<0.001[S]
Fold change	2606.50±1200.64	4788.31±2223.37	0.009[S]

T test was *: significant at $p \leq 0.05$
N: number of cases; SD: standard deviation; S: significant; NS= Non significant

Table 2 demonstrated the mean differences of the selected biomarkers (FOXA2, MicroRNA-590, and Fold change) and compared their levels between the ovarian cancer patient group and the control group.

The mean level of FOXA2 in ovarian cancer patients was 3.09. In the control group, the mean FOXA2 level was 3.72. A T-test revealed a statistically significant difference between the groups ($p = 0.025$). results were also shown a highly significant difference which observed in the mean Ct. MicroRNA-590. Ovarian cancer patients exhibited a Ct. MicroRNA-590 of 19.21 ± 11.86, while the control group showed a significantly increased of 5.25 ± 2.95 ($p < 0.001$)

On the other hand, the Fold change value of MicroRNA-590 in ovarian cancer patients was 2606.50, and in the control, group was 4788.31. The T-test indicated a statistically significant difference between these means ($p = 0.009$).

Table 3. Mean differences of CBC parameters between Ovarian cancer patients & control groups.

Biomarker	Patients N=70	Control N=35	P value
PLT	236.67±115.87	270.74±44.34	0.225[NS]
MPV	8.71±1.25	9.44±1.07	0.031 [S]
HGB	11.72±1.48	12.59±2.53	<0.001[S]
MCV	86.85±7.08	84.68±4.99	0.217[NS]
HCT	36.99±9.60	38.51±4.23	0.550[NS]
WBC	5.92±2.63	6.72±1.99	0.1[NS]
LYM%	36.56±15.62	34.40±8.22	0.0.07[NS]
GRA%	53.99±16.95	57.59±8.93	0.150[NS]

T test was *: significant at $p \leq 0.05$
N: number of cases; SD: standard deviation; S: significant; NS= Non significant

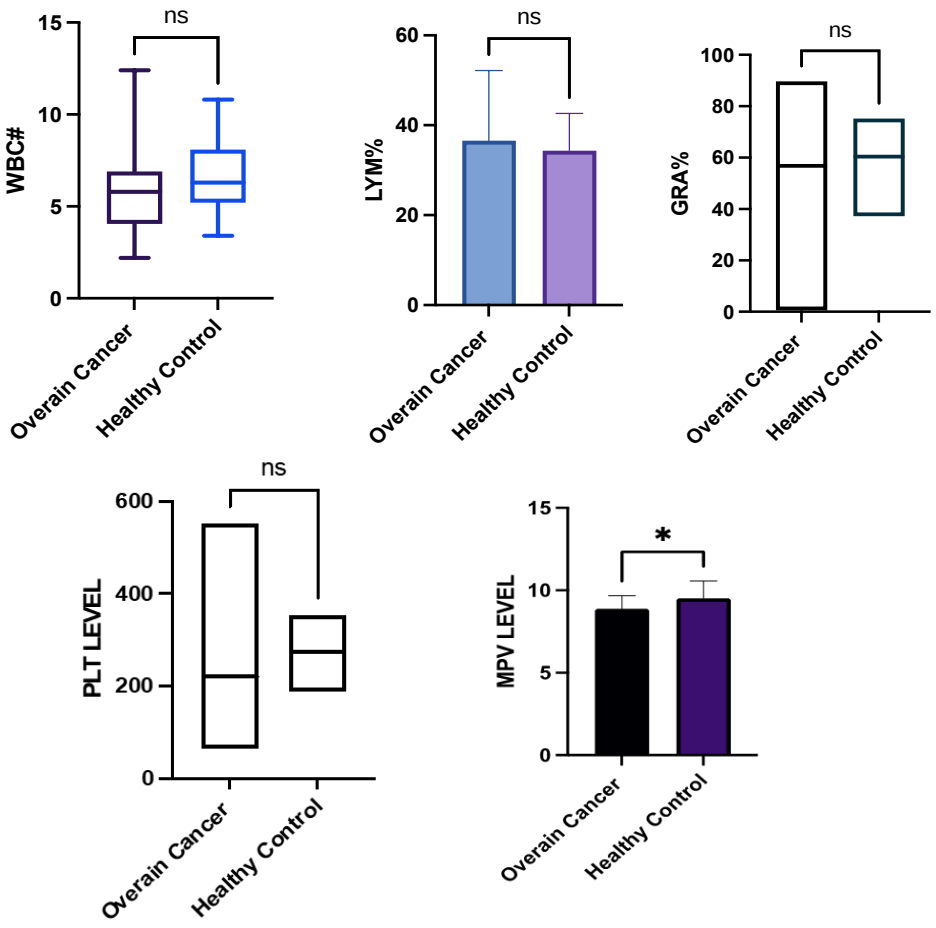

Figure 1. Mean differences of White Blood Cell Subtypes (WBC, LYM%, GRA%) & Platelet Parameters (PLT, MPV) in Ovarian cancer patients & control groups.

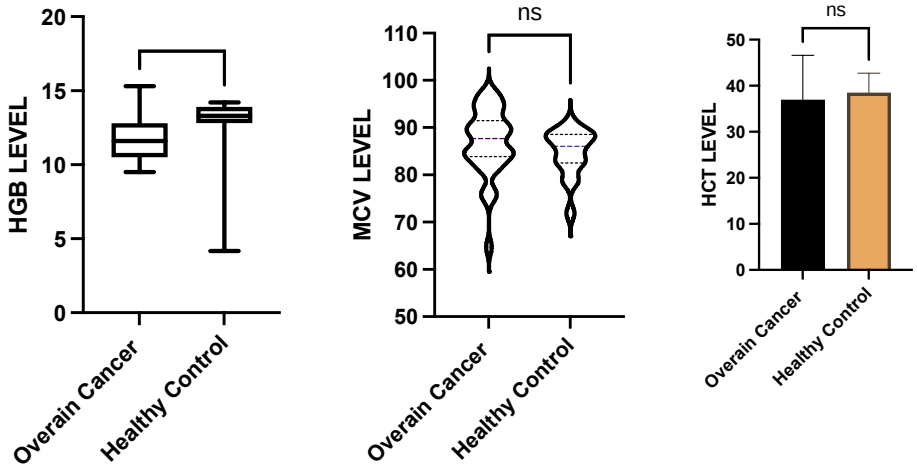

Figure 2. Mean differences hemoglobin and hemoglobin indices (Mean Corpuscular Volume (MCV), Hematocrit (HCT) in Ovarian cancer patients & control groups.

Table 3 & Figure 1,2 presented the mean differences of Complete Blood Count (CBC) parameters between the ovarian cancer patient group and the control group. Overall, Ovarian cancer patients had a statistically lower mean MPV, WBC count compared to the control group, and increased mean Lymphocyte Percentage (LYM%). The mean

differences for Platelet Count (PLT), Mean Corpuscular Volume (MCV), Hematocrit (HCT), and Granulocyte Percentage (GRA%) were not statistically significant between the two groups.

The mean platelet count in ovarian cancer patients was 236.67 ± 115.87 (x10^9/L), while in the control group it was 270.74 ± 44.34 (x10^9/L). The p-value for the comparison between the groups was 0.225, which is not statistically significant

Ovarian cancer patients had a mean MPV of 8.71 ± 1.25 fL, and the control group had a mean MPV of 9.44 ± 1.07 fL. The T-test revealed a statistically significant difference between the groups ($p = 0.031$)

The mean hemoglobin level in ovarian cancer patients was 11.72 ± 1.48 g/dL, and in the control group it was 12.59 ± 2.53 g/dL. The p-value for the comparison between the groups was ($p < 0.001$).

The mean MCV in ovarian cancer patients was 86.85 ± 7.08 fL, and in the control group it was 84.68 ± 4.99 fL. The p-value for the comparison between the groups was 0.217. Ovarian cancer patients had a mean hematocrit of 36.99 ± 9.60%, while the control group had a mean hematocrit of 38.51 ± 4.23%. The p-value for the comparison between the groups was 0.550. The mean white blood cell count in ovarian cancer patients was 5.92 ± 2.63 (x10^9/L), and in the control group it was 6.72 ± 1.99 (x10^9/L). The T-test revealed a statistically non-significant difference between the groups.

Ovarian cancer patients had a mean lymphocyte percentage of 36.56 ± 15.62%, while the control group had a mean lymphocyte percentage of 34.40 ± 8.22%. a statistically non-significant difference between the groups was found.

The mean granulocyte percentage in ovarian cancer patients was 53.99 ± 16.95%, and in the control group it was 57.59 ± 8.93%. The p-value for the comparison between the groups was (0.150).

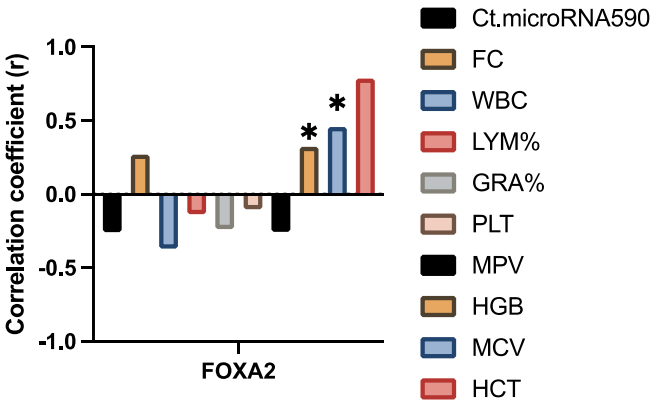

Figure 3. The correlation coefficient (r) between FOXA2 & Serum Levels of biomarkers among Ovarian cancer patients.

Figure 3 shows that FOXA2 has weak to moderate positive correlations with HCT, MCV, and HGB, suggesting a link with red blood cell parameters. It also shows weak negative correlations with WBC, LYM%, and GRA%, indicating a subtle inverse relationship with immune cell profile. Correlations with PLT and MPV were weak, suggesting minimal influence. Additionally, FOXA2 showed a weak negative correlation with Ct.miR-590 and a positive one with fold change (FC), implying a modest association with these circulating factors.

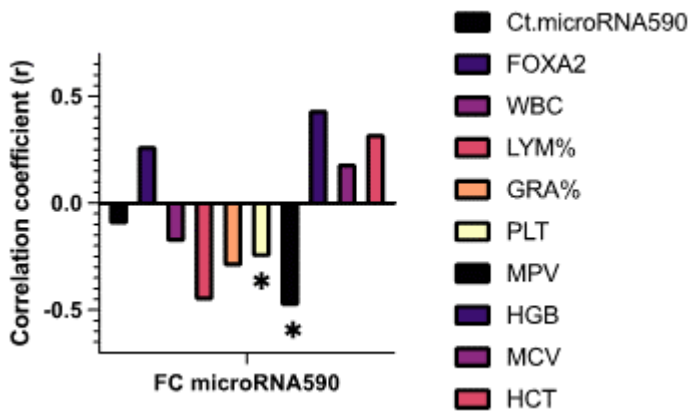

Figure 4. The correlation coefficient (r) between FC microRNA590 & Serum Levels of biomarkers among Ovarian cancer patients.

On the other hand, The correlation analysis indicates that FC microRNA590 levels exhibit varying degrees of association with the measured serum biomarkers in ovarian cancer patients, as presented in Figure 4. The most notable inverse relationships were the weak negative correlations with lymphocyte percentage (LYM%) and mean platelet volume (MPV). This indicated that higher levels of FC microRNA590 tend to be associated with lower percentages of lymphocytes in the blood and smaller average platelet size in this patient group. Weak negative correlations were also observed with total white blood cell count (WBC), granulocyte percentage (GRA%), and platelet count (PLT), indicating a less pronounced inverse trend. The correlation with Ct.microRNA590 was very weak, suggesting minimal linear association between these two circulating microRNA

Further positive correlations were found between FC microRNA590 and hemoglobin (HGB) and hematocrit (HCT), illustrated that higher levels of FC microRNA590 tend to be associated with higher levels of these red blood cell parameters. Weak positive correlations were observed with FOXA2 and mean corpuscular volume (MCV), indicating a less pronounced direct trend.

Table 4 presents the results of binary logistic regression analyses examining the association of each biomarker (FOXA2, MicroRNA-590, and Fold change) with the presence of ovarian cancer disease. The table displays the Odds Ratio (OR) with its 95% Confidence Interval (Lower-Upper) and the corresponding p-value for each biomarker.

Table 4. The binary logistic regression of biomarkers in Ovarian cancer disease.

Variable	OR (Lower-Upper	P value
FOXA2	1.113 (0.917-1.350)	<0.001
MicroRNA-590	1.243(1.079-1.433)	<0.001
Fold change	1.002 (0.142-1.53)	<0.001

p<0.05 considered significantly different- [S]= Significant, [NS]= Non significant, OR= odd ratio

The Odds Ratio for FOXA2 was 1.113, with a 95% Confidence Interval ranging from 0.917 to 1.350. The p-value for this association was <0.001, indicating a statistically significant relationship. The Odds Ratio of 1.113 suggests that for every one-unit increase in FOXA2 level, the odds of having ovarian cancer disease increase by approximately

11.3%. The Odds Ratio for MicroRNA-590 was 1.243, with a 95% Confidence Interval ranging from 1.079 to 1.433. The p-value for this association was <0.001, indicating a statistically significant relationship. The Odds Ratio for Fold change was 1.002, with a wide 95% Confidence Interval ranging from 0.142 to 1.53. The p-value for this association was <0.001, indicating a statistically significant relationship.

Table 5 & Figure 5 presents the Receiver Operating Characteristic (ROC) curve analysis results for FOXA2 levels in predicting ovarian cancer cases compared to a control group. The key metrics for evaluating its diagnostic performance include the Area Under the Curve (AUC), optimal threshold, sensitivity, and specificity.

Table 5. AUC, optimal threshold, Sensitivity, and specificity of FOX A2 levels to analyze the optimal.

Test Variable	AUP	Sensitivity %	Specificity %	Youden index	Cut-off points	CI (95%)
fox a2	51.9%	63.8%	54.2%	0.18	2.45	0.369- 0.669

diagnostic points for predicting such cases compared to control group.

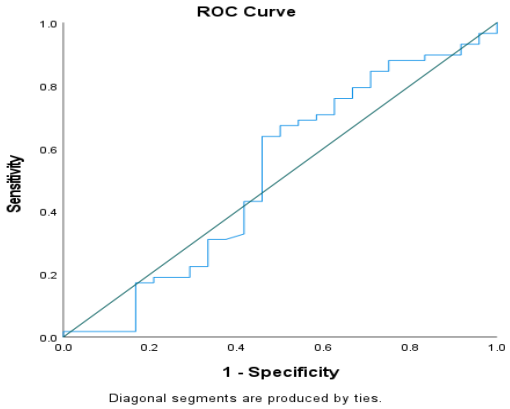

Figure 5. ROC curves of fox a2 serum levels in Ovarian cancer patients to analyze the optimal diagnostic points for predicting such cases compared to control group.

The AUC for FOXA2 was 51.9% (95% CI: 0.369 - 0.669). This value is very close to 50%, which represents no discriminatory power beyond random chance. The confidence interval further indicates a wide range of potential AUC values, encompassing the possibility of FOXA2 being a slightly worse than random predictor to moderately better. Overall, the AUC suggests that FOXA2 levels alone have poor accuracy in distinguishing between individuals with and without ovarian cancer in this study.

The optimal cut-off point for FOXA2 levels was determined to be 2.45. This threshold represents the value that best balances sensitivity and specificity in this dataset.

At the cut-off of 2.45, the sensitivity of FOXA2 for predicting ovarian cancer was 63.8%. This indicates that if this threshold were used, it would correctly identify 63.8% of individuals who actually have ovarian cancer (true positives). However, this also means that 36.2% of individuals with ovarian cancer would be missed (false negatives).

At the same cut-off of 2.45, the specificity of FOXA2 was 54.2%. This indicates that the test would correctly identify 54.2% of individuals who do not have ovarian cancer (true negatives). Conversely, 45.8% of individuals without ovarian cancer would be incorrectly classified as having the disease (false positives).

Table 6 & Figure 6 presents the Receiver Operating Characteristic (ROC) curve analysis results for Fold change values in predicting ovarian cancer cases compared to a control group. The key metrics for evaluating its diagnostic performance include the Area Under the Curve (AUC), optimal threshold, sensitivity, and specificity.

Table 6. AUC, optimal threshold, Sensitivity, and specificity of Fold change values to analyze the optimal.

Test Variable	AUP	Sensitivity %	Specificity %	Youden index	Cut-off points	CI (95%)
Fold change	72.2%	90%	66.7%	0.567	7.929	0.498- 0.947

diagnostic points for predicting such cases compared to control group.

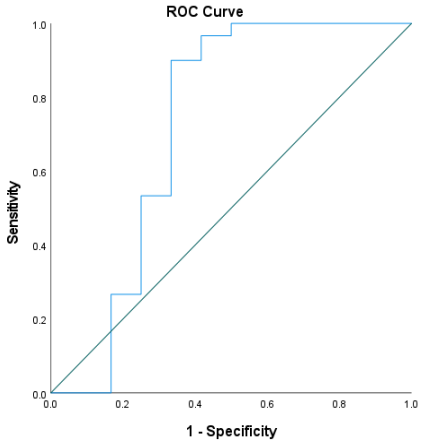

Figure 6. ROC curves of FC microRNA590 serum levels in Ovarian cancer patients to analyze the optimal diagnostic points for predicting such cases compared to control group.

The AUC for Fold change was 72.2%, with a 95% Confidence Interval (CI) of 0.498 - 0.947. This AUC value indicates a fair to good ability of Fold change to discriminate between individuals with and without ovarian cancer.

The optimal cut-off point for Fold change values was determined to be 7.929. This threshold represents the value that best balances sensitivity and specificity in this dataset.

At the cut-off of 7.929, the sensitivity of Fold change for predicting ovarian cancer was 90%. This indicates that if this threshold were used, it would correctly identify 90% of individuals who actually have ovarian cancer (true positives). Only 10% of individuals with ovarian cancer would be missed (false negatives).

At the cut-off of 7.929, the specificity of Fold change was 66.7%. This indicates that the test would correctly identify 66.7% of individuals who do not have ovarian cancer (true negatives). Conversely, 33.3% of individuals without ovarian cancer would be incorrectly classified as having the disease (false positives).

Table 7 & Figure 7 presents the Receiver Operating Characteristic (ROC) curve analysis results for Ct. MicroRNA-590 levels in predicting ovarian cancer cases compared

to a control group. The key metrics for evaluating its diagnostic performance include the Area Under the Curve (AUC), optimal threshold, sensitivity, and specificity.

Table 7. AUC, optimal threshold, Sensitivity and specificity of Ct. Micro RNA590 to analyze the optimal diagnostic points for predicting such cases compared to control group.

Test Variable	AUP	Sensitivity %	Specificity %	Youden index	Cut-off points	CI (95%)
Micro RNA	84.5%	94.1%	72.2%	0.663	8.97	0.720- 0.970

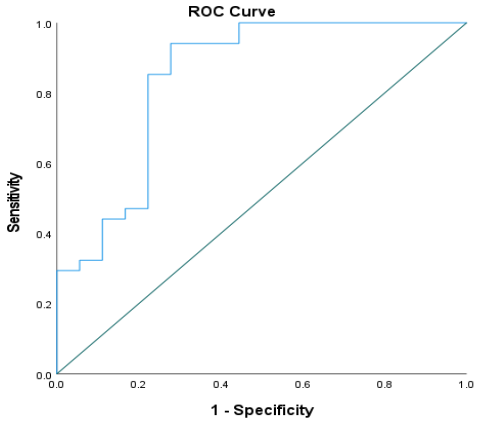

Figure 7. ROC curves of microRNA590 serum levels in Ovarian cancer patients to analyze the optimal diagnostic points for predicting such cases compared to control group.

The AUC for MicroRNA-590 was 84.5%, with a 95% Confidence Interval (CI) of 0.720 - 0.970. This AUC value indicates a very good ability of MicroRNA-590 to discriminate between individuals with and without ovarian cancer. The confidence interval is relatively narrow and entirely above 0.7, suggesting a robust and reliable discriminatory power.

The optimal cut-off point for MicroRNA-590 levels was determined to be 8.97. This threshold represents the value that best balances sensitivity and specificity in this dataset.

At the cut-off of 8.97, the sensitivity of MicroRNA-590 for predicting ovarian cancer was 94.1%. This indicates that if this threshold were used, it would correctly identify 94.1% of individuals who actually have ovarian cancer (true positives). Only 5.9% of individuals with ovarian cancer would be missed (false negatives).

At the cut-off of 8.97, the specificity of MicroRNA-590 was 72.2%. This indicates that the test would correctly identify 72.2% of individuals who do not have ovarian cancer (true negatives). Conversely, 27.8% of individuals without ovarian cancer would be incorrectly classified as having the disease (false positives).

The Youden index, calculated as Sensitivity + Specificity - 1, provides a single measure of the test's overall effectiveness. The Youden index for MicroRNA-590 was 0.663, which is a good value. This suggests a strong discriminatory power of MicroRNA-590 at this optimal cut-off.

4. Discussion

MicroRNAs are small endogenous noncoding RNAs that play a pivotal role in regulating gene expression, and dysregulation of miRNAs has been shown to be associated

with tumorigenesis. Circulating miRNAs are emerging as promising noninvasive biomarkers for the diagnosis and prognosis of various cancers. Among these, MicroRNA-590 has been studied for its role in promoting cell proliferation and survival through its interaction with tumor suppressors such as cyclin G2 in ovarian cancer [10]. In this study, a statistically significant difference was observed in the Ct values of MicroRNA-590 between ovarian cancer patients and healthy controls, with patients exhibiting significantly lower Ct values, indicating higher expression levels. These findings are consistent with previous studies reporting that miR-590 is overexpressed in ovarian cancer and plays an oncogenic role [12].Furthermore, the fold change values of MicroRNA-590 showed a statistically significant decrease in the patient group compared to controls. This suggests that MicroRNA-590 may serve as a useful diagnostic biomarker in distinguishing ovarian cancer patients from healthy individuals [11].

FOXA2, a member of the Forkhead box (FOX) transcription factor family, is known to act as a tumor suppressor gene in several cancers, including ovarian cancer. In this study, FOXA2 levels were significantly lower in the ovarian cancer group than in the control group, supporting previous reports that FOXA2 expression is downregulated in ovarian tumors [18]. The inverse relationship observed between FOXA2 and MicroRNA-590 aligns with previous studies suggesting that miR-590 may target FOXA2, contributing to tumor progression [16-17]. This regulatory relationship may play a role in the development and aggressiveness of ovarian cancer and warrants further investigation.

The correlation analysis in this study showed weak to moderate associations between FOXA2 and hematological parameters, particularly a positive correlation with hematocrit (HCT), mean corpuscular volume (MCV), and hemoglobin (HGB), while negative correlations were observed with WBC, LYM%, and GRA%. These findings may reflect the physiological status of patients or the influence of the tumor microenvironment. On the other hand, Fold change values of MicroRNA-590 were positively correlated with HGB and HCT and negatively correlated with lymphocyte percentage and mean platelet volume (MPV), which may further support its involvement in systemic changes associated with ovarian cancer.

In Table 5-7 the ROC curve analysis further supports the diagnostic value of MicroRNA-590, with an AUC of 84.5%, a sensitivity of 94.1%, and a specificity of 72.2%, indicating a very good diagnostic ability. In contrast, FOXA2 showed a lower diagnostic performance with an AUC of 51.9%, suggesting limited utility as a standalone marker. Binary logistic regression analysis demonstrated statistically significant associations of MicroRNA-590, FOXA2, and fold change with ovarian cancer, reinforcing the potential of these biomarkers in disease prediction and diagnosis Table 4.

5. Conclusion

The current study's findings demonstrated that, in comparison to healthy control samples, ovarian cancer serum had lower levels of FOXA2 and MicroRNA-590. MicroRNA-590 and serum FOXA2 levels may be used as predictive and diagnostic indicators. The diagnostic value of MicroRNA-590 and FOXA2 was validated by the ROC curve and binary logistic regression, with MicroRNA-590 demonstrating the highest diagnostic accuracy.

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