RESEARCH ARTICLE

Determination of ROC Curve based diagnostic strength of miRNA in ovarian cancer

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Abstract

Objective: To examine the diagnostic accuracy of 10 serum-derived micro ribonucleic acids in the early detection of ovarian cancer.

Method: The cross-sectional, comparative study was conducted at the Department of Physiology and Cell Biology, University of Health Sciences, Lahore, Pakistan, from February 6, 2018, to August 1, 2021, and comprised women aged 20-70 years diagnosed with ovarian cancer and tentatively planned for surgical procedures. Serum micro ribonucleic acid levels were analysed using quantitative reverse transcription polymerase chain reaction. Data was analysed using SPSS 24, while the micro ribonucleic acid expression profile was analysed using GraphPad Prism.

Results: There were 24 women with mean age 44±9.92 years. Cancer antigen 125 had a positive correlation with HSA-miR519d-5p, HSA-miR378-3p, HSA-miR16-5p and HSA-miR21-5p ($p<0.05$). The diagnostic value of HSA-miR16-5p and HSA-miR21-5p improved from CA125 baseline to CA125 follow-up (6 months after surgery but before chemotherapy), with an area under the curve of 0.56 and 0.82, respectively. The area under the curve for diagnosing cancer stages based on HSA-miR16-5p and HSA-miR21-5p was 0.37 and 0.70, respectively.

Conclusion: Cancer-specific micro ribonucleic acids, such as HSA-miR21-5p and HSA-miR16-5p, were found to have diagnostic potential, and could be used in combination with cancer antigen 125 for the screening of ovarian cancer.

Key Words: Micro ribonucleic acid, miRNA, Correlation, Expression, Ovarian cancer, CA125.

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Introduction

The incidence of ovarian cancer has become increasingly prevalent.[1] The five-year survival rate of this disease is significantly higher (90%) when detected at an early stage compared to a mere 30% for those diagnosed in International Federation of Gynecology and Obstetrics (FIGO) stages III and IV.[2] Therefore, the emphasis is on early detection to prevent aggressive metastasis and to overcome drug resistance. To achieve this goal, it is crucial to understand the underlying cellular mechanisms of ovarian cancer.[3] In recent years, there has been growing interest in the use of specific micro ribonucleic acids (miRNAs) for the diagnosis of ovarian cancer.[2] Further research is needed to explore the precise role of these miRNAs in the development of ovarian cancer. MiRNAs are small molecules with a wide range of cellular functions, and are produced endogenously.[4] They are synthesised in the nucleus as primary miRNAs, which are then exported to the cytoplasm and processed by the dicer enzyme into a 22 nucleotide small molecule to form mature miRNA.

These miRNAs are expressed differently in tissues, and are involved in various cellular mechanisms through interaction with multiple genes.[5] MiRNAs play a role in multiple cellular processes, such as the cell cycle, cell proliferation, development, differentiation, apoptosis and metabolism.[4] The first reported connection between miRNA and a disease was chronic lymphocytic leukaemia.[2] Since then, many studies.[3-5] have revealed the important functions of miRNAs in various cellular processes. The abnormal pattern adopted by tumour cells is the result of interactions between previously normal and healthy tissue along with its surrounding supporting cells and tissue. For tumour development and progression, numerous factors, including immune, hormonal and cellular, play a crucial role. Among these factors, miRNAs are emerging as important tools due to their diagnostic, prognostic and therapeutic potential in various human cancers.

The cancer antigen 125 (CA125) biomarker is a heavily glycosylated transmembrane mucin that is elevated in 50% of cases of early-stage ovarian cancer, and in 70-90% of advanced-stage ovarian cancer cases.[6] It is cleaved outside the cell membrane and then released into body fluids, making it easily detectable for providing disease

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information. However, the traditional use of CA125 as a diagnostic or prognostic biomarker is unreliable due to its lack of specificity for epithelial ovarian cancer. CA125 is altered in many cancers.[7] The need for new, specific, non-invasive and economical biomarkers have encouraged the exploration of disease-specific miRNAs. The current study was planned to investigate 10 miRNAs associated with epithelial ovarian cancer, and to determine the sensitivity and specificity of HSA-miR16-5p and HSA-miR21-5p.

Materials and Methods

Ethical review board of University of Health Sciences Lahore (UHS/REG-17/ERC 4659) had given approval to conduct this study in accordance with Helsinki declaration of human rights [8]

The cross-sectional, comparative study was conducted at the Department of Physiology and Cell Biology, University of Health Sciences (UHS), Lahore, Pakistan, from February 6, 2018, to August 1, 2021.

The sample size was calculated using the following formula[9]:

$$n = \frac{2\sigma^2(z_{1-\alpha/2} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

Where, the level of significance was 5, power of test 95%, population standard deviation 1, population variance 1, test value of population mean 2, and anticipated population mean 1.

The subjects were recruited from the Institute of Nuclear Medicine and Oncology (INMOL), Lahore, Sheikh Zayed Hospital, Lahore, Hijaz Hospital, Lahore, and Fatima Memorial Hospital, Lahore. Convenient sampling technique was used. Blood sample. (2.5 ml) was taken from patients of Ovarian Cancer who fulfilled the inclusion criteria.

Those included were women aged 20-70 years who had been diagnosed with ovarian cancer and were tentatively planned for surgical procedures, including unilateral or bilateral oophorectomy, salpingo-oophorectomy via laparotomy or laparoscopy, subtotal resection, or removal of tumour fragments, and hysterectomy with salpingo-oophorectomy. Those already on chemotherapy were excluded.

The sample was stratified into those aged <55 years and those aged >55 years. Likewise, the patients were classified into malignant (serous, mucinous, endometroid, clear cell, and mixed) and borderline (borderline serous, cytoadeno, papillary serous, endometroid adeno, papillary adeno, borderline serous, adeno, cytology positive mucinous papillary) groups. On the basis of body mass index (BMI), the sample was divided into obesity class I (25-29kg/m^2) and obesity class II (>30kg/m2).[10] Baseline and follow-up CA125 levels were obtained from patient medical reports. After a thorough literature review and analysis with the help of bioinformatic tools,[10] miRNAs were selected[11] that were involved in the regulation of genes in the PI3K/AKT/mTOR pathway in ovarian cancer.

Quantification of miRNAs was performed using quantitative reverse transcription-polymerase chain reaction (qRT-PCR). The results were analysed using receiver operating characteristic (ROC) curves to estimate the diagnostic usefulness of the miRNA serum levels.

A miRNA isolation kit (Invitrogen, mirVana; Catalogue No AM1561, USA) was used to extract total RNA and miRNA from white blood cells (WBCs) in accordance with the manufacturer's instructions. Nanodrop 2000 (Catalogue No ND-2000, Thermo-Scientific, USA) was used to measure the amount of miRNA, and the A260/A280 (absorbence Ratio) value was used to determine purity.

The complementary deoxyribonucleic acid (cDNA) of miRNA was produced using a kit (miScript II RT Kit, Qiagen, USA). Unlike RNA profiles, the miRNA thermocycler profiles were set to incubate at 37°C for 60 minutes, and then at 95°C for 5 minutes as per the manufacturer's instructions. The produced cDNA of miRNA was stored at -20°C. PCR test was conducted on the cDNA of the genes using housekeeping gene primers, such as B-Actin and GAPDH, followed by verification using 2% agarose gel electrophoresis. The expression of miRNA was then analysed using RT-PCR.

To analyse miRNA expression levels, gene-specific primers were utilised (Table 1). The expression levels of miRNA genes were measured using a real-time PCR detection

Table-1: List of micro ribonucleic acid (miRNA) primers used.

No.	Name	Sequence
1	HSA-miR-210-3p	GTTTCTGTGCGTGTGACAG
2	HSA-miR -126-3p	GGGTCGTACCGTGAGTAAT
3	HSA-miR -378-3p	GTGACTGGACTTGGAGTCA
4	HSA-miR -519d-5p	GTTTCCTCCAAAGGGAAGC
5	HSA-miR -519d-3p	GTGCAAAGTGCCTCCCTTT
6	HSA-miR -16-5p	GTTTGGTAGCAGCACGTAAATA
7	HSA-miR -122-5p	GTGTGGAGTGTGACAATGG
8	HSA-miR -21-5p	GTTTGGTAGCTTATCAGACTGA
9	HSA-miR -182-5p	GTTGTTTGGCAATGGTAGAACT
10	HSA-miR -376c	AACATAGAGGAAATTCCACG
11	U6 forward	CTCGCTTCGGCAGCACA
12	U6 reverse	AACGCTTCACGAATTTGCGT

system (CFX96, Catalogue No KO22, Thermoscientific's, USA) as per the manufacturer's recommendations. Three biological and technical replicates of each relative expression experiment were performed for each set of miRNA genes and the housekeeping gene U6. The statistical analysis was carried out using GraphPad Prism[8].

The PCR reaction conditions involved an initial denaturation step at 94°C for 5 minutes, followed by amplification for 35 cycles with annealing at 58°C for 35 seconds and extension at 72°C for 35 seconds, and the final extension step at 72°C for 5 minutes.

Data was analysed using SPSS 24. Mean and standard deviation values were computed for quantitative variables, while frequencies and percentages were calculated for categorical variables. A box plot was generated to visualise the distribution of miRNAs. Mann Whitney U test was applied to compare the categories of cancer stage, age and tumour type based on miRNA expression levels. Spearman correlation was calculated between CA125 and miRNA. ROC curves were generated to evaluate the area under the curve (AUC)for HSA-miR16-5p and HSA-miR21-5p based on FIGO stage. P<0.05 was considered significant.

Results

Of the 24 subjects, 20(83.3%) were aged <55 years (Table 2), while the overall mean age was 44±9.92 years

Table-2: Clinical characteristics of the patients.

Parameter	Type	Frequency	Percentage
Tumour	Malignant	15	62.5
	Borderline	9	37.5
Age	< 55 Years	20	83.3
	≥55 Years	4	16.7
BMI	Obesity class I (25-29)	7	29.2
	Obesity class II (>30)	17	70.8
Marital	Unmarried	6	25.0
	Married	18	75.0
FIGO Stage	Stage I	9	37.5
	Stage II	3	12.5
	Stage III	6	25.0
	Stage IV	6	25.0
CA 125	Baseline	13	54.2
	Follow up	11	45.8
CA 125 Follow-up	Normal (<35)	7	29.2
	Abnormal (>35)	17	70.8

∗CA125 Baseline is value recorded from available laboratory reports at time of recruitment but before surgery

∗CA125 Follow-up is value recorded from available laboratory reports done 6-8 months after surgery

BMI: Body mass index, FIGO: International Federation of Gynaecology and Obstetrics, CA: Cancer antigen.

Table-3: Mean value of patient characteristics

Variables	Mean	±Std. Deviation
Height	154.63	3.59
Weight	66.42	13.52
BMI	27.80	5.67
Age	44.63	9.92
CA 125 baseline	869.88	1381.48
CA 125 Follow-up	55.79	52.34

∗CA125 Baseline is value recorded from available laboratory reports at time of recruitment but before surgery

∗CA125 Follow up is value recorded from available laboratory reports done 6-8 months after surgery

BMI: Body mass index, CA: Cancer antigen.

Table-4: Comparison of up-regulated and down-regulated miRNA.

Sr.No.	miRNA	Fold change (>1)	miRNA	Fold change (<1)
1	HSA-miR519d-3p	1.05	HSA-miR 519d-5p	0.20
2	HSA-miR 16-5p	2.13	HSA-miR 126-3p	0.14
3	HSA-miR 21-5p	12.5	HSA-miR 182-5p	0.43
4	HSA-miR 376c	2.12	HSA-miR 122-5p	0.34
5	HSA-miR 210-3p	1.13	HSA-miR 378-3p	0.11

The table shows the comparison of miRNA with fold expression <1 and >1
miRNA: micro ribonucleic acid.

(Table 3).

The expression profiling of the 10 selected miRNAs showed 5(50%) with upregulated (>1 fold) expression, with the highest expression being HSA-miR21 (12.5 fold).

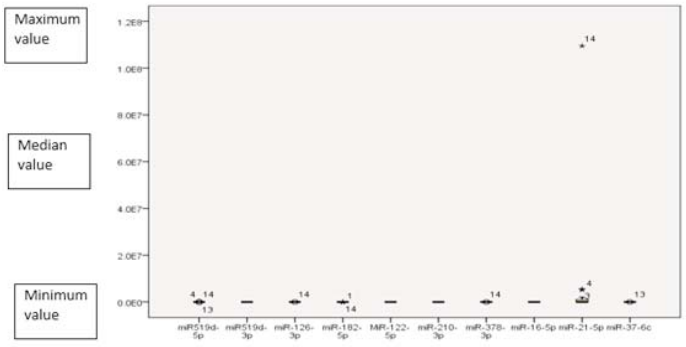

Figure-1: Box plot of micro ribonucleic acid (miRNA) expression

Additionally, 5(50%_ miRNAs were found to be down-regulated (<1 fold) (Table 4, Figure 1).

CA125 baseline had the highest correlation with HSA-miR378-3p, while CA125 follow-up value had the highest correlation with HSA-miR122-5p. The association between miRNA and CA125 was significant for HSA-miR519d-5p (p=0.007) at baseline and follow-up

Table-5: Correlation of CA125 with micro ribonucleic acids (miRNAs).

miRNA	CA 125 Baseline		CA 125 Follow up	
	Correlation Coefficient	p-Value	Correlation Coefficient	p-Value
HSA-miR 519d-5p	0.37	0.07	0.52	0.009
HSA-miR 519d-3p	0.25	0.24	0.06	0.764
HSA-miR -126-3p	0.12	0.57	-0.18	0.391
HSA-miR -182-5p	-0.04	0.87	0.27	0.192
HSA-miR -122-5p	0.26	0.22	0.019	0.934
HSA-miR -210-3p	0.35	0.09	0.064	0.767
HSA-miR -378-3p	0.39	0.056	0.53	0.008
HSA-miR -16-5p	0.13	0.55	0.48	0.017
HSA-miR -21-5p	0.26	0.34	0.58	0.023
HSA-miR -376c	0.35	0.08	0.18	0.389

(p=0.009). Additionally, the correlation between CA125 baseline and HSA-miR378 was moderately significant for HSA-miR378-3p (p=0.05). For CA125 follow-up (6 months after surgery but before chemotherapy), HSA-miR378-3p (p=0.008), HSA-miR16-5p (p=0.017) and HSA-miR21-5p (p=0.023) were also statistically significant. Positive and significant correlations were found for HSA-miR210-3p (p=0.09) and HSA-miR378-3p (p=0.05) with CA125 baseline. However, a negative correlation was found

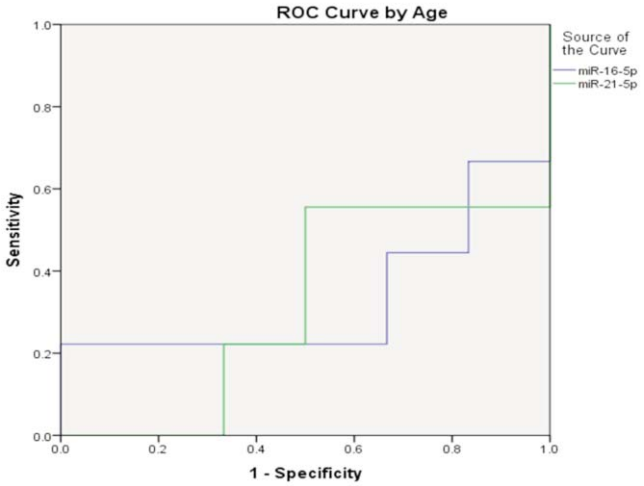

Figure-2: Receiver operating characteristic (ROC) curve for HSA-miR 16-5p and HSA-miR 21-5p for age groups

between HSA-miR182-5p and CA125 baseline, with correlation coefficient -0.04 (p=0.87) (Table 5).

Positive correlations were found for CA125 follow-up values with HSA-miR519d-5p, HSA-miR378-3p, HSA-miR16-5p and HSA-miR21-5p (p=0.009, p=0.008, p=0.017 and p=0.023, respectively). Conversely, a negative correlation was found between HSA-miR126-3p and CA125 follow-up value with correlation coefficient -0.18

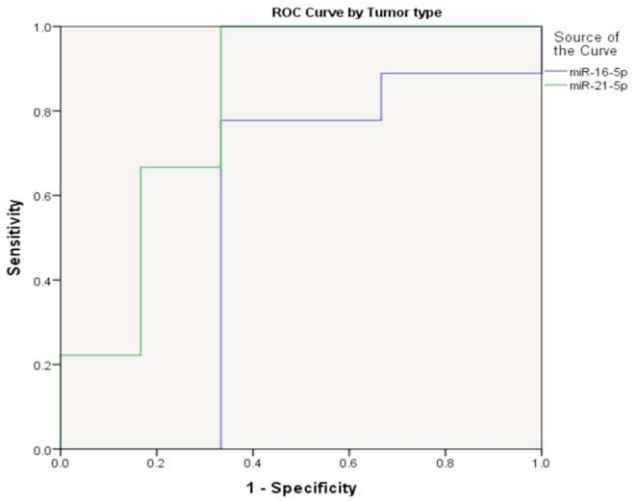

Figure-3: Receiver operating characteristic (ROC) curve for HSA-miR16-5p and HSA-miR21-5p for type of cancer

(p=0.39).

HSA-miR16-5p had the ability to differentiate between age groups (Figure 2), while HSA-miR21-5p has the ability to distinguish between malignant and borderline ovarian cancer and between early and advanced tumour stages

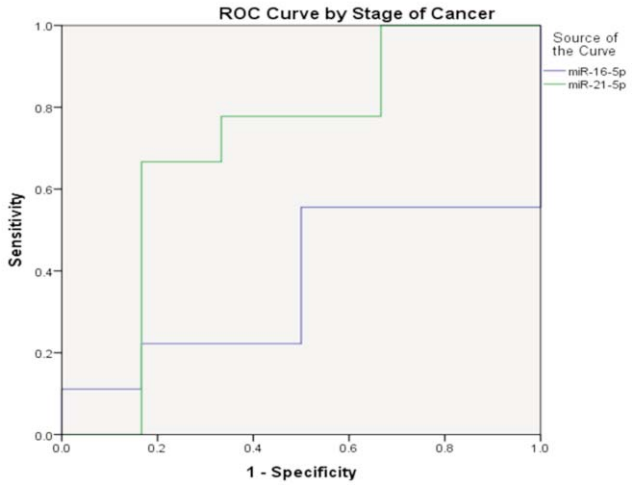

Figure-4: Receiver operating characteristic (ROC) Curve for HSA-miR16-5p and HSA-miR21-5p for International Federation of Gynaecology and Obstetrics (FIGO) stage of cancer

(Figure 3). AUC value 0.37 for HSA-miR16-5p showed the ability to differentiate on the basis of tumour stage (Figure 4).

Discussion

To our knowledge, the current study is the first of its kind in Pakistan and highlights the significance of the role of

miRNAs in the development of ovarian cancer cases. In the study, the mean age of ovarian cancer patients was 44 years, with 83.3% of the cases aged <55 years. This was in contrast to a previous study that reported a mean age of 62.7 years (range: 21-78 years).[12] In terms of FIGO stages, the current study had 37.5% cases of stage I, 12.5% stage II, 25% stage III, and 25% stage IV. A previous study, however, reported 17.8% of stage I, 8.9% stage II, 55.5% stage III, and 17% stage IV[12]. The current study also determined that 70.8% of the patients had CA125 level >35, while 29.2% had it <35. One study that found 7.2% of patients with CA125 level <35 and 3.9% with 35 and 65. Another research found that 82.2% of women affected by cancer had a CA125 level >65[6].

The HSA-miR519 is involved in resistance to cisplatin.[13] The current study found that the levels of HSA-mir519d-5p were down-regulated, while HSA-miR 519d-3p was up-regulated. This finding agrees with a previous study which reported down regulation of HS-mir519d in lung cancer.[14] The current study also noted the under-expression of HSA-miR126-5p, which is in contrast to another study that found elevated levels of HSA-miR126 in ovarian cancer.[15]

HSA-miR182 is correlated with FOX and AKT genes and plays a role in cell proliferation and growth as well as in tumour invasion and metastasis.[5] The current study found under-expression of HSA-mir182-5p (p=0.9), which contradicts another research that presented its overexpression (p<0.0001)[16]. Several studies[2,5,6,17] have also reported overexpression of HSA-mir182-5p.

HSA-miR378 interacts with tumour promoter genes[3] and works with Smad. The loss of Smad can facilitate cancer metastasis.[13] The current study found under-expression of HSA-miR378-5p, which contradicts another study that reported its overexpression in ovarian cancer,.[13] HSA-miR 210 confers resistance to radiotherapy by inhibiting apoptosis, and is part of E2F.[18] It promotes proliferation, migration and invasion by AKT16. The current study found overexpression of HSA-miR210-3p (p=0.9), which agrees with another research that found elevated levels of HSA-miR210 (p<0.05).[19]

The current study discovered down-regulation of HSA-miR122-5p (p=0.07), which is consistent to earlier studies that reported under-expression of HSA-miR122-5p (p=0.007).[20] The finding of up-regulated HSA-miR16-5p is partially in agreement with another research that showed similar expression levels in ovarian cancer and healthy cases.[21,22]

This research focussed on the role of HSA-miR21 and HSA-miR376 in ovarian cancer. HSA-miR21 has been identified as an oncomiR, and functions by reducing the expression of tumour suppressor genes, such as PTEN. Inhibition of HSA-miR21 has been shown to promote cancer cell apoptosis by targetting the PI3K/AKT/PTEN signalling pathway.[23] This study found that HSA-miR21-5p was up-regulated (p=0.045), which is consistent with previous research[20], Studies done in 2008[24] and 2013[22] reported raised serum levels of HSA-miR21[24], and the current results are in line with such findings. HSA-miR376 has been found to promote chemoresistance.[25] This study noted the up-regulation of HSA-miR376c, which contradicts earlier reports that found under-expression of HSA-miR376 in ovarian cancer[6]

The current study also analysed the AUC of HSA-miR16-5p and HSA-miR21-5p for malignant and borderline groups of ovarian cancer, and found values of 0.56 and 0.82, respectively. Another study reported a sensitivity of 86% and a specificity of 85% for HSA-miR16 and HSA-miR21 in epithelial ovarian cancer compared to healthy women.[20] The current results are consistent with earlier research that found overexpression of HSA-miR16 and HSA-miR21, and highlighted their diagnostic potential.[26] However, miRNAs also serve as prognostic biomarkers as their varying levels indicate the progression or regression phase of the disease, as well as their sensitivity to treatment.[2]

Gao et al. in 2015 identified miRNAs in ovarian cancer patients, and explained the AUC using an ROC curve for the miR200 family, proposing the use of miRNAs as prognostic tools. The reference criteria for a biomarker to be considered significant for diagnosis or prognosis include specificity 99.6%, sensitivity 75%, and positive predictive value (PPV) 10%.[27] The current results in contrast may be explained with respect to differences in the population, histological type of ovarian tumour, and the microenvironment that recruits multiple miRNAs with oncogenic or tumour suppressor functions in a single instant.

The current study has limitations as the sample size was small and the distribution of FIGO stages of ovarian cancer were inconsistent.

Conclusion

Cancer-specific miRNAs, such as HSA-miR21-5p and HSA-miR16-5p, were found to have diagnostic potential, and could be used in combination with CA125 for the screening of ovarian cancer.

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AUTHOR'S CONTRIBUTION:

RH: Wrote up synopsis of the research, took samples, performed experiment, data analysis, writing and responsible for integrity of research.

SK: Data analysis, critically improved intellectual content and supervised the research.